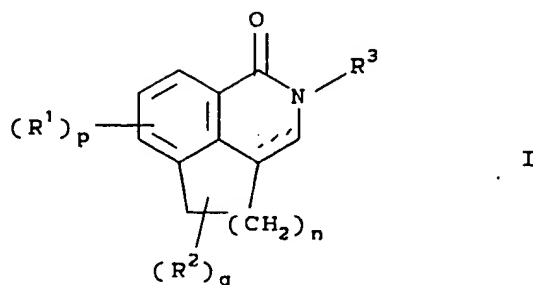


WE CLAIM:

1. A compound of Formula I



10 in which

the dashed line denotes an optional double bond;

n is 1, 2 or 3;

p is 0, 1, 2 or 3;

15 q is 0, 1 or 2;

each R¹ is independently selected from halogen, hydroxy, lower alkoxy (optionally substituted with phenyl), lower alkyl, nitro, amino, amino-carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;

20 each R² is lower alkyl; and

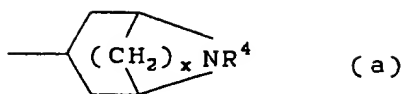
R³ is selected from

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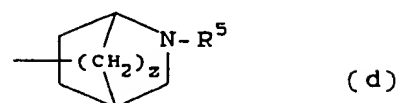
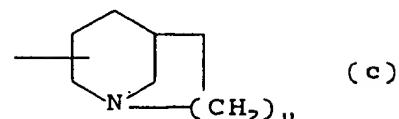
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10



15



in which

u, x, y, and z are all independently an integer from 1 to 3; and

R⁴ and R⁵ are independently C₁₋₇ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₂ alkyl, or a group (CH₂)_tR₆ where t is 1 or 2 and R₆ is thienyl, pyrrolyl or furyl optionally further substituted by one or two

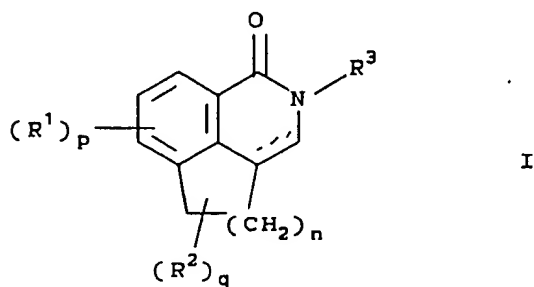
substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C₁₋₄ alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C₁₋₄ alkyl (optionally

substituted by hydroxy, C₁₋₄ alkoxy, carboxy, esterified carboxy or *in vivo* hydrolyzable acyloxy); or a pharmaceutically acceptable salt thereof or an *N*-oxide thereof; or

an individual isomer or mixture of isomers thereof.

SUMMARY OF THE INVENTION

In a first aspect, this invention provides a compound of Formula I:



in which

the dashed line denotes an optional double bond;

n is 1, 2 or 3;

p is 0, 1, 2 or 3;

q is 0, 1 or 2;

each R¹ is independently selected from halogen,

hydroxy, lower alkoxy (optionally substituted

with phenyl), lower alkyl, nitro, amino, amino

carbonyl, (lower alkyl)amino, di(lower

alkyl)amino, and (lower alkanoyl)amino;

each R² is lower alkyl; and

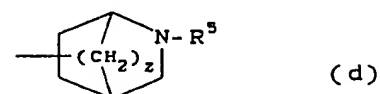
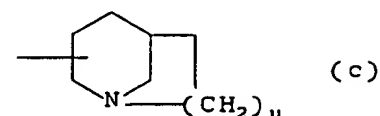
R³ is selected from



5



10



in which

15

u, x, y and z are each independently an integer from 1 to 3; and

20

R⁴ and R⁵ are independently C₁₋₇ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₂ alkyl, or a group (CH₂)_tR₆ where t is 1 or 2 and R₆ is thienyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C₁₋₄ alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C₁₋₄ alkyl (optionally substituted by hydroxy, C₁₋₄ alkoxy, carboxy, esterified carboxy or *in vivo* hydrolyzable acyloxy); or

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a pharmaceutically acceptable salt thereof or N-oxide derivative thereof, or an individual isomer or mixture of isomers thereof.

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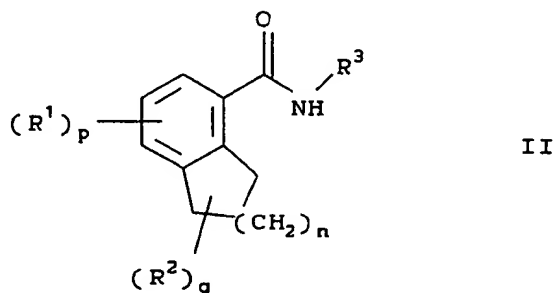
In a second aspect, this invention provides a pharmaceutical composition which contains a compound of Formula I, preferably in admixture with one or more suitable excipients.

5 In a third aspect, this invention provides a method of treating emesis, gastrointestinal disorders, CNS disorders including cognitive performance disorders and drug dependency, cardiovascular disorders or pain by administering a therapeutically effective amount of a
10 compound of Formula I to a subject afflicted with such a condition.

In a fourth aspect, this invention provides compounds of Formula II which are useful intermediates for preparing compounds of Formula I:

15

20



25 wherein n, p, q, R¹, R² and R³ are as defined for Formula I.

A fifth aspect of this invention is a process for preparing compounds of Formula I and is set forth in the "Detailed Description Of The Invention."

30

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DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise stated, the following terms used
5 in the specification and claims have the meanings given
below:

"Alkyl" means a straight or branched saturated
hydrocarbon radical having from one to the number of
carbon atoms designated. For example C₁₋₇ alkyl is
10 alkyl having at least one but no more than seven carbon
atoms, e.g. methyl, ethyl, *i*-propyl, *n*-propyl, *n*-butyl,
pentyl, heptyl and the like.

"Lower alkyl" means an alkyl of one to six carbon
atoms.

15 "Lower alkoxy", "(lower alkyl)amino", "di(lower
alkyl)amino", "(lower alkanoyl)amino", and similar terms
mean alkoxy, alkylamino, dialkylamino, alkanoylamino,
etc. in which the or each alkyl radical is a "lower
alkyl" as described above.

20 "Halogen" means fluorine, chlorine, bromine, or
iodine. Preferred halogens are chlorine and bromine;

"Pharmaceutically acceptable" means that which is
useful in preparing a pharmaceutical composition that is
generally safe and non-toxic and includes that which is
25 acceptable for veterinary use as well as human
pharmaceutical use.

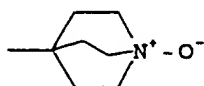
"Pharmaceutically acceptable salts" means salts
which possess the desired pharmacological activity and
which are neither biologically nor otherwise
30 undesirable. Such salts include acid addition salts
formed with inorganic acids such as hydrochloric acid,
hydrobromic acid, sulfuric acid, nitric acid, phosphoric
acid, and the like; or with organic acids such as acetic
acid, propionic acid, hexanoic acid, heptanoic acid,

35

cyclopentanepropionic acid, glycolic acid, pyruvic acid,
lactic acid, malonic acid, succinic acid, malic acid,
maleic acid, fumaric acid, tartaric acid, citric acid,
benzoic acid, o-(4-hydroxy-benzoyl)benzoic acid,
5 cinnamic acid, mandelic acid, methanesulfonic acid,
ethanesulfonic acid, 1,2-ethanedisulfonic acid,
2-hydroxyethanesulfonic acid, benzenesulfonic acid,
p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic
acid, p-toluenesulfonic acid, camphorsulfonic acid,
10 4-methyl-bicyclo[2.2.2]oct-2-ene-1-carboxylic acid,
glucoheptonic acid,
4,4'-methylenebis(3-hydroxy-2-naphthoic) acid,
3-phenylpropionic acid, trimethyl-acetic acid, tertiary
butylacetic acid, lauryl sulfuric acid, gluconic acid,
15 glutamic acid, hydroynaphthoic acid, salicylic acid,
stearic acid, muconic acid, and the like. Preferred
pharmaceutically acceptable salts are those formed with
hydrochloric acid.

The compounds of Formula I with a R¹ hydroxy group
20 are capable of forming salts with inorganic or organic
bases. Preferred pharmaceutically acceptable bases
include sodium hydroxide, sodium carbonate, potassium
hydroxide, aluminum hydroxide, calcium hydroxide and
organic bases such as diethanolamine, tromethamine,
25 N-methylglucamine, ethanolamine, triethanolamine and
others.

"N-oxide derivative" of a compound means the form
of a compound of Formula I wherein the nitrogen of the
R³ moiety of Formula I is in the oxidized state, e.g.



In defining the subject matter of this invention reference is made in the structure to substituents $(R^1)_p$ and $(R^2)_q$. It should be noted that the list of substituents of R^1 and R^2 does not include hydrogen, and each of p and q can be 0. It is to be understood that when p or q is 0, the respective ring structures will not be substituted and thus will have only hydrogens around the ring.

"Animal" includes humans, non-human mammals (such as dogs, cats, rabbits, cattle, horses, sheep, goats, swine, and deer) and non-mammals such as birds and the like.

"Disease" specifically includes any unhealthy condition of an animal or part thereof and may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e. the "side effects" of such therapy. Thus, "disease" here includes the nausea and emesis caused by therapy with agents having emetogenic side effects, in particular by therapy for cancer, such as chemotherapy with cytotoxic agents and radiotherapy.

"Treatment" means any treatment of a disease in an animal and includes:

- (1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display symptoms of the disease,
- (2) inhibiting the disease, i.e. arresting its development, or
- (3) relieving the disease, i.e. causing regression of the disease.

"Effective amount" for a disease means that amount which, when administered to an animal in need thereof, is sufficient to effect treatment, as defined above, for that disease.

Certain compounds of Formula I and Formula II may exist as optical isomers. In the compounds of the invention, any isomer or mixture of isomers may be used and the claims are intended to cover the individual isomer and mixtures thereof, unless otherwise
5 restricted. The invention includes all optical isomers of any asymmetrical compound of Formula I, as well as mixtures thereof.

"Isomerism" refers to compounds having the same atomic mass and atomic number but differing in one or
10 more physical or chemical properties. Various types of isomers include the following:

"Stereoisomer" refers to a chemical compound having the same molecular weight, chemical composition, and
15 constitution as another, but with the atoms grouped differently. That is, certain identical chemical moieties are at different orientations in space and, therefore, when pure, have the ability to rotate the plane of polarized light. However, some pure
20 stereoisomers may have an optical rotation that is so slight that it is undetectable with present instrumentation.

"Optical isomer" describes one type of stereo isomerism which manifests itself by the rotation that
25 the isomer, either pure or in solution, imparts to the plane of polarized light. It is caused in many instances by the attachment of four different chemical atoms or groups to at least one of the carbon atoms in a molecule.

Stereoisomers or optical isomers that are mirror
30 images of one another are termed "enantiomers" and may be said to be enantiomeric. Chiral groups that are mirror images of one another are termed enantiomeric groups.

Enantiomers whose absolute configurations are not known may be differentiated as dextrorotatory (prefix +) or laevorotatory (prefix -) depending on the direction in which, under specified experimental conditions, they rotate the plane of polarized light.

When equal amounts of enantiomeric molecules are present together, the product is termed racemic, independently of whether it is crystalline, liquid, or gaseous. A homogeneous solid phase composed of equimolar amounts of enantiomeric molecules is termed a racemic compound. A mixture of equimolar amounts of enantiomeric molecules present as separate solid phases is termed a racemic mixture. Any homogeneous phase containing equimolar amounts of enantiomeric molecules is termed a racemate.

"Diastereoisomer" refers to stereoisomers some or all of which are dissymmetric but which are not mirror images of each other. Diastereoisomers corresponding to a given structural formula must have at least two asymmetric atoms. A compound having two asymmetric atoms will usually exist in four diastereoisomeric forms, i.e. (-)-erythro, (+)-erythro, (-)-threo and (+)-threo.

The optically active compounds herein can be designated by a number of conventions; i.e., the *R*- and *S*-sequencing rules of Cahn and Prelog; erythro and threo isomers; *D*- and *L*-isomers; *d*- and *l*-isomers; and (+) and (-) isomers, which indicates the direction a plane of polarized light is rotated by the chemical structure, either pure or in solution. These conventions are well known in the art and are described in detail by E.L. Eliel in Stereochemistry of Carbon Compounds, published by McGraw Hill Book Company, Inc. of New York in 1962 and references cited therein. Thus,

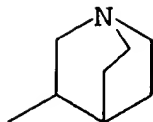
these isomers may be described as d-, l-, or a d,l-pair; or D-, L-, or a D,L-pair; or R-, S-, or an R,S-pair; depending upon the nomenclature system employed. In general, this application will use the (R), (S) and (RS) designation.

5 "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted
10 phenyl" means that the phenyl may or may not be substituted and that the description includes both unsubstituted phenyl and phenyl wherein there is substitution; "optionally followed by converting the
15 free base to the acid addition salt" means that said conversion may or may not be carried out in order for the process described to fall within the invention, and the invention includes those processes wherein the free base is converted to the acid addition salt and those
20 processes in which it is not.

Certain R³ substituents are of particular interest for the compounds of this invention and are therefore defined specifically. In some cases the R³ substituent will exhibit a chiral center at the ring carbon which is
25 bonded to the amide nitrogen. It is to be understood that a straight line representing the covalent bond between the chiral carbon and the amide nitrogen is understood to represent either the R or S configuration, or a mixture (not necessarily racemic) thereof. These
30 R³ substituents of particular interest are as follows:

(1) subformula (b) where y is 2 having the specific formula

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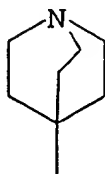


is referred to as 1-azabicyclo[2.2.2]oct-3-yl;

10

(2) subformula (b) where y is 2 having the specific formula

15

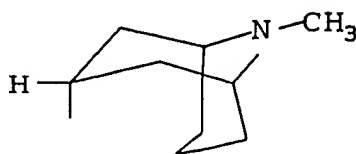


is referred to as 1-azabicyclo[2.2.2]oct-4-yl;

20

(3) subformula (a) where x is 3 and R⁴ is methyl having the specific formula

25



is referred to as

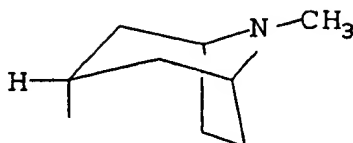
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endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;

35

(4) subformula (a) where x is 2 and R⁴ is methyl having the specific formula

5



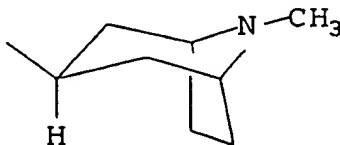
is referred to as

10

endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;

(5) subformula (a) where x is 2 and R⁴ is methyl having the specific formula

15



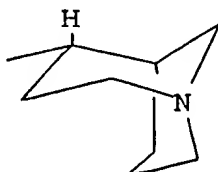
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is referred to as

exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; and

(6) subformula (c) wherein u is 2 having the specific formula

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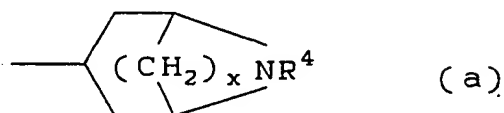
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carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;

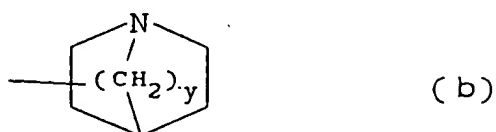
each R^2 is lower alkyl; and

R^3 is selected from

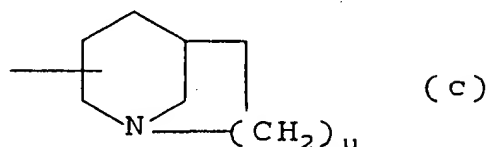
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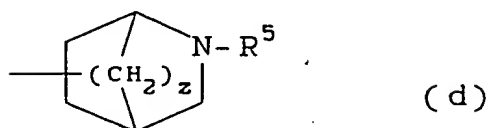
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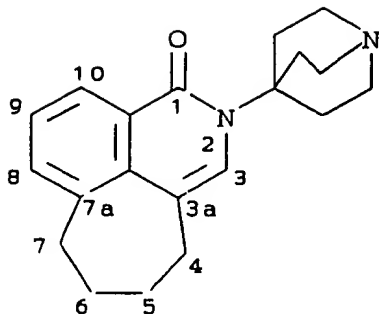


in which

u , x , y and z are all independently an integer from 1 to 3; and

R^4 and R^5 are independently C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-2} alkyl, or a group $(CH_2)_t R_6$ where t is 1 or 2 and R_6 is thienyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two

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5
10 is named 2-(azabicyclo[2.2.2]oct-4-yl)-
1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one.

Utility

The compounds of this invention, as defined by
Formula I, exhibit pharmaceutical activity and in
15 particular 5-HT₃ receptor antagonist activity. As such,
these compounds are useful for treating a broad range of
conditions in animals, particularly humans, in which the
5-HT₃ receptor plays a role. Examples of conditions that
may be treated using the compounds of this invention
20 include emesis, gastrointestinal disorders, central
nervous system (CNS) disorders including cognitive
performance disorders, drug dependency, etc.,
cardiovascular disorders and pain.

For purposes of this patent application,
25 particularly the claims the term "emesis" will have a
meaning that is broader than the normal, dictionary
definition and includes not only vomiting, but also
nausea and retching. Such a condition of emesis may be
induced by or result from the administration of
30 chemotherapeutic or cytotoxic agents or radiation in
cancer treatment or from the exposure to radiation,
surgical operations or anesthesia or motion sickness
(caused by riding in a vehicle, airplane, vessel, etc.).

35

The compounds of this invention can be referred to as anti-emetics and are particularly valuable for treating (especially preventing) emesis induced in cancer patients by treatments with cytotoxic pharmaceutical agents or radiation. Such cytotoxic agents include platinum anti-cancer agents such as cisplatin (cis-diamminedichloroplatinum), as well as non-platinum anti-cancer drugs such as cyclophosphamide (cytoxan), vincristine (leurocristine), procarbazine (N-(1-methylethyl)-4-[(2-methylhydrazino)methyl]-benzamide), methotrexate, fluorouracil, mechlorethamine hydrochloride (2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride), doxorubicin, adriamycin, dactinomycin (actinomycin-D) cytarabine, carmustine, dacarbazine, and others listed at page 1143 of the Journal of Clinical Oncology 1989; 7(8): 1143.

The compounds of the invention may also be useful for treating post-operative nausea and vomiting and motion sickness and for the treatment of all conditions described hereinbefore.

The compounds of Formula I are useful in the treatment of gastrointestinal disorders (e.g. of the stomach, esophagus and both the large and small intestines). Examples of specific conditions that may be treated using the compounds of this invention include, but are not limited to, dyspepsia (including non-ulcer dyspepsia), gastric stasis, peptic ulcer, reflux esophagitis, flatulence, bile reflux gastritis, pseudo-obstruction syndrome, irritable colon syndrome (which may result in chronic constipation or diarrhea), diverticular disease, biliary dysmotility (which may result in sphincter of Oddi dysfunction and "sludge" or microscopic crystals in the gall bladder), gastroparesis (e.g. diabetic, postsurgical or idiopathic), irritable

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5 bowel syndrome and retarded gastric emptying. The compounds of the invention are also useful as short-term prokinetics to facilitate diagnostic radiology and intestinal intubation. In addition the compounds are useful for treating diarrhea, particularly diarrhea induced by cholera and carcinoid syndrome.

10 The compounds of Formula I are useful in treating CNS disorders. Some of the categories of treatable CNS disorders include cognitive disorders, psychoses, anxiety/depression and obsessive/compulsive behavior. Cognitive disorders include attentional or memory deficit, dementia states (including senile dementia of the Alzheimer's type and aging), cerebral vascular deficiency and Parkinson's disease. Psychoses that may be treated using the compounds of this invention include
15 paranoia and schizophrenia. Representative, treatable anxiety/depressive states include anticipatory anxiety (e.g. prior to surgery, dental work, etc.), depression, mania, convulsions and anxiety caused by withdrawal from
20 addictive substances such as nicotine, alcohol, common narcotics, cocaine and other drugs of abuse. Finally obsessive/compulsive behavior, e.g. that which results in obesity, may be treated using the compounds of this invention.

25 Cardiovascular disorders that may be treated using a compound of this invention are those that are mediated by the presence of serotonin. Examples of such disorders include arrhythmias and hypertension.

30 It is thought that the compounds of this invention prevent certain adverse nervous transmissions and/or prevent vasodilation and thus reduce the perceived level of pain. Examples of pain treatable using a compound of this invention include cluster headaches, migraines,

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trigeminal neuralgia and visceral pain (e.g. that caused by abnormal distension of hollow visceral organs).

To determine the 5-HT₃ antagonist activity of compounds of this invention one of ordinary skill may use the Rat Cerebral Cortex Binding Assay, a predictive
5 *in vitro* assay which assesses the binding affinity of a compound for the 5-HT₃ receptor. The method is described in Kilpatrick, G.J., Jones, B.J. and Tyers, M.B., Nature 1987; 330: 24-31. The assay as adapted for
10 testing compounds of the invention and results are set out in Example 11 of this application. The compounds of Formula I exhibit affinity for the 5-HT₃ receptor in this assay.

The von Bezold-Jarisch test for 5-HT₃ antagonist activity in rats is an accepted test for determining
15 5-HT₃ antagonist activity *in vivo* by measuring the von Bezold-Jarisch reflex in anesthetized rats. See, e.g., Butler, A., Hill, J.M., Ireland, S.J., Jordan, C.C., Tyters, M.B., Brit. J. Pharmacol. 1988; 94: 397-412; Cohen, M.L., Bloomquist, W., Gidda, J.S., Lacefield, W.,
20 J. Pharmacol. Exp. Ther. 1989; 248: 197-201; and Fozard, J.R., MDL 72222: Arch. Pharmacol. 1984; 326: 36-44. The compounds of the invention exhibit activity in the von Bezold-Jarisch test. The details of the
25 procedure (as modified for testing the compounds of the invention) and results are set out in Example 14 of this application. Compounds of Formula I reduce cisplatin-induced emesis in the ferret.

The cisplatin-induced emesis test in ferrets is an accepted test for determining anti-emetic activity
30 *in vivo*, see e.g. Costall, B., Domeney, A.M., Naylor, R.J., and Tattersall, F.D., Neuropharmacology 1986; 25(8): 959-961; and Miner, W.D. and Sanger G.J., Brit. J. Pharmacol. 1986; 88: 497-499. A general
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description and results are set out in Example 13 of this application. Compounds of Formula I reduce cisplatin-induced emesis in the ferret.

5 Anti-emetic properties in the control of emesis in dogs due to administration of platinum anti-cancer drugs are also determined by a modification of the method described by Smith, W.L., Alphin, R.S., Jackson, C.B., and Sancilio, L.F., J. Pharm. Pharmacol. 1989; 41: 101-105; and Gylys, J.A., Res. Commun. Chem. Pathol. Pharmacol. 1979; 23(1): 61-68 as follows: cisplatin (cis-diamminedichloroplatinum) is administered at a dose of 3 mg/kg intravenously to non-fasted dogs (both sexes). Sixty minutes after cisplatin administration, the test drug in saline at a dose volume of 0.1 ml/kg is administered intravenously. A control group of dogs is given the cisplatin followed by saline at 60 min, without test drug. The dogs are observed continuously for a period of 5 hr counting the number of emetic episodes and comparing them to emetic episodes observed for the controls.

20 The utility for treating gastrointestinal disorders is determined by assaying the gastrokinetic pharmacological activity using the method of Droppleman, D., Gregory, R., and Alphin, R.S., J. Pharmacol. Methods 1980; 4(3): 227-30 wherein the rate of emptying of a test meal in rats compared to controls was observed. The Droppleman et al. method is an accepted method for determining gastrointestinal activity *in vivo*. The compounds of the invention exhibit activity in the Droppleman et al. method, the detail of which is set out in Example 12. The compounds of Formula I show activity in this assay.

30 The utility for treatment of a CNS disorder such as anxiety (anxiolytic activity) is determined by the

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art-recognized Crawley and Goodwin two-compartment exploratory model as described in Kilfoil, T., Michel, A., Montgomery, D., and Whiting, R.L., Neuropharmacology 1989; 28(9): 901-905. In brief, the method involves determining whether a compound reduces the natural anxiety of mice in brightly-lit areas. Compounds of the invention are active in this art recognized test. An example is set forth in Example 15 of this application. Compounds of Formula I are active in this test.

Cognition enhancing activity may be determined by the mouse habituation/cognitive enhancement test. See procedures described in Barnes, J.M., Costall, B., Kelly, M.E., Naylor, F.J., Onaivi, E.S., Tomkins, D.M. and Tyers, M.B. Br. J. Pharmacol. 98, 693P (1989). This procedure utilizes the exploratory model described above to test for improvements in the impaired cognitive performance of aged mice. A detailed description is set forth in Example 18 of this application. Compounds of Formula I enhance cognitive performance in this test.

Anxiolytic activity during withdrawal from drugs of abuse is determined by the mouse light/dark withdrawal anxiety test. This procedure utilizes the exploratory model described above to test for anxiolytic activity after administration and subsequent abrupt cessation of alcohol, cocaine or nicotine treatments. A detailed description is set for in Example 17 of this application. Compounds of Formula I are effective at reversing the drug withdrawal-induced anxiety in this test.

All of the aforementioned citations to *in vitro* and *in vivo* methods for determining activity of the compounds of this invention and other documents cited herein are incorporated herein by reference.

In summary then another aspect of this invention is a method for treating an animal exhibiting a condition in which the 5-HT₃ receptor plays a role, e.g. where the condition is chosen from emesis, a gastrointestinal disorder, a CNS disorder, a cardiovascular disorder and pain, which method comprises administering a therapeutically effective amount of a compound of Formula I to such mammal. The compounds are particularly valuable for treating humans.

A therapeutically effective amount of a compound is an amount that is efficacious in treating the condition, i.e. the disease. The exact amount administered may vary over a wide range depending on the degree of severity of the specific condition being treated, age of the subject, relative health of the subject and other factors. A therapeutically effective amount may vary from about 0.000001 mg (1 nanogram [ng]) per Kg body weight per day to about 10.0 mg/Kg body weight per day. Preferably the amount will be about 10 ng/Kg/day to about 1.0 mg/Kg/day, especially for anti-emetic purposes. Thus, for a 70 Kg human, a therapeutically effective amount may be from about 70 ng/day to 700 mg/day, preferably about 700 ng/day to about 70 mg/day.

Administration and Pharmaceutical Composition

The compounds of this invention may be administered via any of the usual and acceptable modes known in the art, either singly or in combination with another compound of this invention or with another therapeutic agent. Generally a compound of this invention is administered as a pharmaceutical composition with a pharmaceutically acceptable excipient and is administered orally, systemically (e.g. transdermally, intranasally or by suppository) or parenterally (e.g. intramuscularly

[im], intravenously [iv] or subcutaneously [sc]). The compounds of the invention can thus be administered in a composition that is a semisolid, powder, aerosol, solution, suspension or other appropriate composition, as discussed hereinafter.

5 A pharmaceutical composition comprises a compound of Formula I, wherein each substituent is defined hereinabove, preferably in combination with a pharmaceutically acceptable excipient. Such excipient is one that is non-toxic and acts to aid in the
10 administration of the compound of this invention. Such excipient may be any solid, liquid, semisolid, gaseous (in case of an aerosol) excipient that is generally available to one of skill in the art and that does not adversely affect the activity of the active agent.

15 In general, the pharmaceutical composition of this invention will contain a therapeutically effective amount of a compound in combination with at least one excipient. Depending on the type of formulation, size of a unit dosage, kind of excipients and other factors known
20 to those of skill in the art of pharmaceutical sciences the amount of compound of this invention may vary over a wide range in the composition. In general, the final composition will comprise about 0.001%w to about 99.5%w of a compound of the invention with the
25 remainder being the excipient or excipients. Preferably the level of active compound will be about 0.01%w to about 10.0% and most preferably about 0.1%w to about 1.0%w, with the remainder being a suitable excipient or
30 excipients.

Useful pharmaceutical excipients for the preparation of the pharmaceutical compositions hereof can be solids, semisolids, liquids or gases. Thus, the compositions can take the form of tablets, pills,

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capsules, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, and the like. Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol, various oils, including those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly for injectable solutions. Compressed gases are frequently used to dispense the active ingredient in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, nitrous oxide, etc. Other suitable pharmaceutical carriers and their formulations are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required.

Presently Preferred Embodiments

While the broadest definition of this invention is set forth in the Summary of the Invention as a compound of Formula I wherein each of n, p, q, R¹, R², R³, R⁴, R⁵, u, x, y and z is defined in its broadest aspect, certain compounds of the invention are preferred. For example, the compounds of Formula I wherein p is 0, 1, or 2; n is 1 or 2; q is 0, R¹ is halogen, lower alkoxy or amino; and if R³ comprises R⁴ and R⁵ they are each lower alkyl or R³ is a bicyclic

substituent as specified in the Summary of the Invention without further substituents. Of this subgroup those of particular interest include compounds of Formula I wherein p is 0, the dashed line represents a double bond and if R³ comprises R⁴ and R⁵ they are each methyl, with particularly preferred compounds being those wherein R³ is 1-azabicyclo[2.2.2]oct-3-yl; 1-azabicyclo-[2.2.2]oct-4-yl; endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl; endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; 10 exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; or endo-1-azabicyclo[3.3.1]non-4-yl. Representative examples are set out in Examples 4 and 5.

Another subgroup of particular interest includes compounds of Formula I wherein n is 1 or 2; p and q are both 0; the dashed line represents 2 hydrogens; and if R³ comprises R⁴ and R⁵ they are each methyl or R³ is a bicyclic substituent as specified above without further substituents. Particularly preferred compounds are those wherein R³ is 1-azabicyclo[2.2.2]oct-3-yl; 1-azabicyclo-[2.2.2]oct-4-yl; endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl; endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; or endo-1-azabicyclo[3.3.1]non-4-yl. Representative 25 compounds are made by following the procedure set forth in Example 7.

Still another subgroup of compounds of particular interest include those of Formula I wherein p is 0, 1 or 2 (especially where p is 0); n is 3; q is 0; R is halogen, lower alkoxy or amino; and if R³ comprises R⁴ and R⁵ they are each lower alkyl (particularly methyl) or R³ is a bicyclic substituent as specified above without further substituents. Of these, compounds where the dashed line is a double bond are of particular 35

interest, particularly those wherein

R^3 is 1-azabicyclo[2.2.2]oct-3-yl;

1-azabicyclo-[2.2.2]oct-4-yl;

endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;

5 endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;

exo-8-methyl- 8-azabicyclo[3.2.1]oct-3-yl; or

endo-1-azabicyclo[3.3.1] non-4-yl. Representative

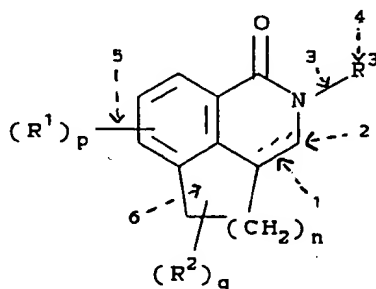
examples are set forth in Example 6.

10 It is understood that these subgroups of particular interest are particularly useful in the pharmaceutical compositions and methods of treatment of this invention.

Processes for Preparing Compounds of the Invention

15 The compounds of Formula I are prepared by a variety of methods. The synthetic approaches are apparent from the numbered dotted lines (1 to 6) in Formula I below. The dotted lines point schematically to the respective reaction sites and the ensuing table gives a brief description of the various methods that will be described in more detail below. The last column in the table and the letter symbols in parentheses refer to the respective step in the process claim(s).

Formula I

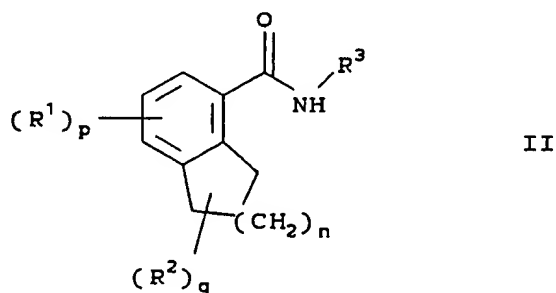


<u>Approach</u>	<u>Method</u>	<u>Step</u>
	1. Hydrogenation	(b)
	2. Formylation	(a)
	3. Alkylation	(d)
	4. N-Oxidation or	(f)
	Amine oxide Reduction	
5	5. Elaboration of Substituent R ¹	(g)
	6. Hydrogenation	(h)
	7.* Salt Formation	(e)
	8.* Liberation of Free Base	(c)
	9.* Optical Resolution	(f)
	10.* Separation of Diastereomers	(i)

*Not shown on Formula I

Accordingly, the process for the preparation of a compound of Formula I comprises one or more of the following steps:

(a) reactively contacting a compound of Formula II



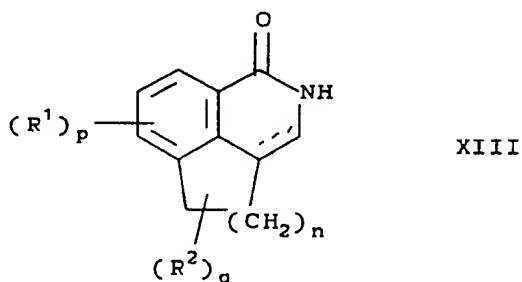
in which n, p, q, R¹, R², and R³ are as defined above with a formylating agent in the presence of a strong

base to form a compound of Formula I wherein the dashed line is a double bond,

(b) reducing the double bond represented by the dashed line in Formula I by hydrogenation to form a compound of Formula I wherein the dashed line represents 2 hydrogens,

(c) converting a salt of a compound of Formula I to the corresponding free compound,

(d) condensing a compound of the formula R^3L , wherein R^3 has the above meanings and L is a leaving group with a compound of the Formula XIII,



wherein R^1 , R^2 , n , p , q , and the dashed line have the above meanings,

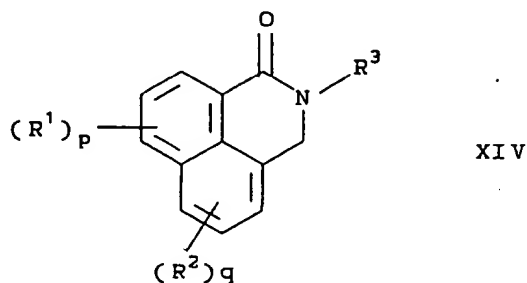
(e) converting a compound of Formula I to the corresponding pharmaceutically acceptable salt,

(f) oxidizing a compound of Formula I to form the corresponding *N*-oxide of the R^3 component of Formula I, or reducing an *N*-oxide of the R^3 component to the corresponding amine,

(g) reducing a R^1 nitro substituent to a R^1 amino substituent or alkylating or acylating a R^1 amino substituent or alkylating a R^1 hydroxy substituent or dealkylating a R^1 alkoxy substituent or debenzylating a

R^1 benzyloxy substituent to the corresponding compound of Formula I,

(h) hydrogenating in positions 3a, 4, 5 and 6 a compound of the Formula XIV



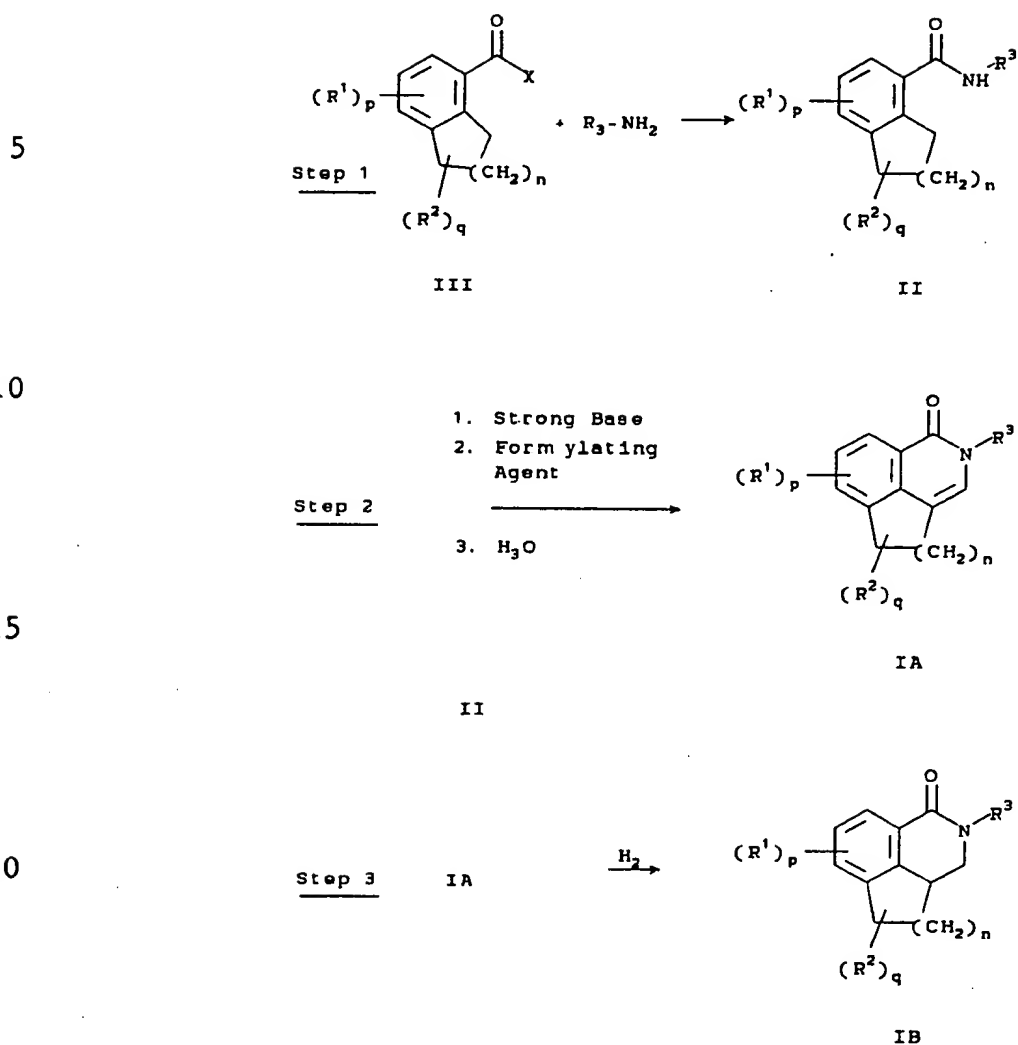
wherein R^1 , R^2 , R^3 , p and q have the above meanings,

(i) separating a mixture of isomers or diastereomers of a compound of Formula I into a single isomer or diastereomer, or

(j) conducting any of steps (a) through (i) with optically active reactants.

In the formylation step, the compounds of Formula I are prepared by the reaction sequence shown below in Reaction Scheme I.

REACTION SCHEME I



25 wherein

X = OH, -OR (R = alkyl) or halogen; and
n, p, q, R¹, R² and R³ are as broadly defined above
in the Summary of the Invention.

30 Step 1

In step 1 of the process of this invention, the
fused-ring bicyclic acid, ester or halide of Formula III

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is reacted with an appropriate amine to form the corresponding amide of Formula II.

In general compounds of Formula III and the amines of Formula R^3NH_2 are known in the art, are commercially available or are prepared in accordance with methods
5 available to those of ordinary skill in the art. For example, the compounds of Formula III where X is OH, p is 1, R^1 is methoxy (particularly meta to the acid), q is 0 and n is 1 or 2 have been reported by Lowenthal, H.J. and Schatzmiller, S., J. Chem. Soc. Perkin Trans. I
10 1976; 944. Unsubstituted compounds (where p and q are both 0, and n is 1, 2 or 3) are readily available or may be prepared in accordance with methods known in the art.

Other starting materials that are useful for
15 preparing compounds of the invention are commercially available 1-cyano-4-alkoxynaphthalenes or 1-cyano-2-alkoxynaphthalenes which can be hydrolyzed and reduced to the corresponding starting acid of Formula III where X is OH, R^1 is 4-alkoxy or 2-alkoxy, q is 0 and n is 2. Halogen-substituted tetralones are
20 well known and are prepared from o-halo- γ -phenylbutyric acids. All these tetralones can be reduced with alkali boranates such as sodium or lithium boranate to the appropriate alcohol (Formula X of Reaction Scheme II), converted to an acid and reacted with the R^3NH_2 compound
25 as a lactone to form an amide of Formula II according to Reaction Scheme II below. Amines of formula R^3NH_2 that are useful in this step include those where R^3 is defined in the Summary of the Invention section of this application. Particularly useful are the amines where
30 R^3 is one of the following radicals:

1-azabicyclo[2.2.2]oct-3-yl;
1-azabicyclo[2.2.2]oct-4-yl;
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;

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endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; or
endo-1-azabicyclo[3.3.1]non-4-yl.

5 The reaction conditions under which Step 1 is
carried out are those conditions that are standard for
amide formation. Generally a solution of the amine in
an inert organic solvent is reacted under normal
conditions such as those set forth in March, J. Advanced
10 Organic Chemistry 1985; 3rd Ed.: 370-376. A
particularly useful method is the reaction of the amide
as a dimethylaluminum amine ($\text{Me}_2\text{AlNHR}^3$) with an alkyl
ester (Formula III) where X is lower alkoxy, such as
ethoxy. Suitable non-reactive, organic solvents
15 (e.g. toluene or dichloroethane) may be used to carry
out the reaction at mild conditions such as ambient
pressure and less than ambient temperature, preferably
temperatures of from about -10°C to about $+20^\circ\text{C}$. The
reaction generally is completed within a few hours.

20 Step 2

In this step the novel, intermediate amide of
this invention shown as Formula II is reacted with a
formylating agent in the presence of a strong base.
25 The reaction is carried out in a non-reactive ethereal
solvent such as diethyl ether, dimethoxyethane or
tetrahydrofuran (THF), the last being preferred.
The formylating agent useful for this reaction is any
compound that achieves reaction of the amide of
30 Formula II with the formyl group ($-\text{CH}=\text{O}$), particularly a
dialkylformamide, such as dimethyl formamide (DMF),
diethyl formamide, etc., a N-aryl-N-alkylformamide, such
as N-phenyl-N-methylformamide, etc. The formylating
agent is generally used in molar excess relative to the

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amide II, for example at a ratio of about 1.1 to about 5.0, with 1.5 to 2.5 being preferred. The strong base useful in this reaction is one that aids the progression of the reaction and can be any appropriate alkyllithium or Grignard reagent. *n*-Butyllithium is particularly
5 useful because of its availability. In general, the reaction takes place under an inert atmosphere (e.g. argon) to prevent the oxidation of the alkyllithium and at a temperature range of about -70°C to ambient temperature. Preferably the temperature is
10 about -20°C to about 0°C, as the reduced temperature is thought to stabilize the intermediate anions formed in this step.

15 Step 3

In this step the double bond (represented by the dashed line in Formula I and specifically shown in Formula IA) is reduced by hydrogenation. This reaction takes place under standard hydrogenation conditions
20 using a standard hydrogenation catalyst under pressure varying from about atmospheric to about 2000 pounds per square inch (psi) and temperatures ranging from about ambient temperature to about 100°C. The hydrogenation takes place in a suitable polar, organic solvent such as
25 ethanol, DMF, acetic acid, ethyl acetate, tetrahydrofuran, toluene, and the like.

While a standard catalyst (e.g. rhodium on alumina, etc.) may be used, particularly useful catalysts are 20% palladium hydroxide on carbon, 10% palladium on carbon, Pearlman's catalyst from Aldrich (50% H_2O ~ 20% palladium
30 content), palladium/ $BaSO_4$. The reduction will take place over a few hours to two or more days depending on the catalyst used, pressure, solvent and temperature. For example using acetic acid with 70% perchloric acid

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and 20% palladium hydroxide on carbon, a compound can be fully reduced in about 24 hours at about 50 psi and about 85°C.

The compound to be reduced can be used as the free base or in the form of a salt selected from the acid addition salts previously described, in particular the hydrochloride, hydrobromide, camphorsulfonate, acetate, etc. If an optically active acid is used this would frequently influence the preferential formation of one isomer.

Preparation of Isomers

From the Formula (I) it is apparent that some of the compounds of the invention may have at least one or two asymmetric carbon atoms (chiral centers). If the dashed line between carbon atoms 3 and 3a denotes a bond, the compounds of Formula I may have one asymmetric carbon atom in the R^3 substituent, i.e., positions 3' or 4' (which are attached to the N-atom denoted as ring atom 2).

Some R^3 substituents, for example, the 1-azabicyclo[2.2.2]oct-4-yl, endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl and the endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl substituents have no asymmetric carbon atom (center of chirality). Therefore, the compounds of Formula I containing an achiral R^3 substituent and a double bond between carbon atoms 3 and 3a are achiral compounds.

If the dashed line between carbon atoms 3 and 3a represents two hydrogen atoms, the compounds of Formula I have at least one asymmetric carbon atom, i.e. the carbon atom numbered 3a. If R^3 is a chiral substituent the compounds of Formula I have two asymmetric carbon atoms.

For the compounds of Formula I which have one asymmetric carbon atom, two enantiomeric forms exist, the (R)- and (S)- form as determined by the rules of Cahn et al.

5 A number of methods suitable for the resolution of enantiomers can be used but the preferred methods depend on the preparation of diastereomeric compounds derived from the enantiomers. While the resolution can be achieved with covalent diastereomeric compounds derived from the compounds of Formula I and diastereomeric
10 complexes, the preferred diastereomeric compounds are dissociable. In general, the covalent diastereomers are separated by chromatography but preferred are separation/resolution techniques depending on
15 differences in solubility.

 In a preferred method the compounds of Formula I with one asymmetric carbon atom are separated by the formation of crystalline diastereomeric salts between the racemic substrate (R, S) and an optically active
20 acid. Examples of suitable resolving agents which form dissociable salts with the enantiomers of formula I are tartaric acid, o-nitrotartranilic acid, mandelic acid, malic acid, 2-phenoxypropionic acid, hydratropic acid and 2-arylpropionic acids in general, or camphorsulfonic
25 acid. Alternatively, selective crystallization, direct crystallization or chromatography can be used. Specifics of the resolution techniques applicable to the preparation of enantiomers of the Formula I are described in Jean Jacques, André Collet, Samuel H.
30 Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

 The compounds of Formula I which have two asymmetric carbon atoms occur as diastereomeric compounds with a total of four isomers, since the first
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asymmetric carbon atom may be R or S, and so may be the second. For example the (3aR,3'R) molecule is the mirror image of the (3aS,3'S) compound, i.e., they are enantiomers. The (3aS,3'R) compound in turn is the enantiomer of the (3aR,3'S) compound. The two pairs of enantiomers stand in the relationship to each other of diastereomers, i.e., they are nonenantiomeric pairs in a set. As enantiomers the (3aR,3'R) compound and the (3aS,3'S) compound have identical physical properties except that they rotate the plane of polarized light in equal amounts in opposite directions. In addition, they react at different rates with other optically active compounds.

The properties of the enantiomers of one diastereomeric pair, however, are not identical with those of the other diastereomeric pair. In other words, the (3aS,3'S) compound has different physical properties from the (3aR,3'S) and the (3aS,3'R) compound. They have different melting points, boiling points, solubilities, reactivity and other properties.

Since the nonenantiomeric pairs that make out the diastereomers have different melting points, boiling points, and solubilities, the pairs can be easily separated by conventional means such as salt formation that allows to apply crystallization techniques based upon differences in solubility. However, the free bases or their salts that form diastereomers can also be separated by chromatographic techniques. Since the diastereomers have different physical properties, no optically active auxillary reagents such as resolving agents need to be employed. For salt formation all the salt-forming acids described above, as long as they form crystalline salts, may be used for the separation techniques. A particular advantage of chromatographic

resolutions is that they provide both diastereomers generally in a state of high purity. Every type of preparative chromatography can be used for the purpose of such diastereomer separation (gravity column, thin-layer, dry-column and high- and medium-pressure liquid chromatography). Specifics of the applicable methodology are described in Jean Jacques, André Collet, Samuel H. Wilen, *Enantiomers, Racemates, and Resolutions*, John Wiley & Sons, Inc. (1981), Chapter 5.

After separation of the two pairs of enantiomers each pair can be resolved into its enantiomers by the methods generally used for the separation of enantiomers, e.g., resolution by direct crystallization which depends on differences in the rates of crystallization of the enantiomers in a supersaturated solution with respect to the racemate. Alternatively, resolving agents and fractional crystallization can be employed as described for the compounds of Formula I with one asymmetric carbon atom.

Alternatively, the compounds of the invention may be prepared using optically active reactants. For example, using (R)-or (S)-amines of the Formula R^3NH_2 (wherein R^3 has the above meanings) individual isomers of the Formula II may be prepared which may be converted to individual isomers of Formulae IA or IB. This is shown by Examples 1A(2), 2A for the amides of Formula II and by Examples 4A(2), 5A,C,D for the compounds of Formula IA and by Example 7 for the compounds of Formula IB.

The stereoconfiguration at the chiral centers of the compounds of Formula I can be assigned by circular dichroism, preferably by Single Crystal X-Ray Analysis.

Other Methods of Preparation

One of ordinary skill in the art will also recognize that a compound of Formula I may be prepared as an acid addition salt or as the corresponding free base. If prepared as an acid addition salt, the compound is converted to the free base by treatment with a suitable base such as ammonium hydroxide solution, sodium hydroxide, potassium hydroxide or the like. When converting a free base to an acid addition salt, the compound is reacted with a suitable organic or inorganic acid (described earlier).

It is also understood that compounds of this invention that are the *N*-oxides of compounds of Formula I (the *N*-oxides of the cyclic amine portion of R^3) are prepared by means known in the art by reacting a compound of Formula I with oxidizing agents such as pertrifluoroacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *m*-chloroperoxybenzoic acid. With *m*-chloroperoxybenzoic acid the oxidation is conducted under cooling in an inert, organic solvent such as a halogenated hydrocarbon, e.g. dichloromethane. For this oxidation to take place effectively, the compound of Formula I is preferably in the free base form.

The *N*-oxides of the compounds of Formula I can also be reduced by methods known in the art. A number of reducing agents are suitable for this purpose, specifically sulfur dioxide, sulfur itself, triaryl phosphines such as triphenyl phosphine, alkali boranates such as lithium or sodium boranate, or phosphorous trichloride or tribromide. The reaction will be conducted at a temperature between 0 and 80°C, with gradual raising of the temperature and the reaction mixture is occasionally shaken. As some of the *N*-oxides have a low melting point the reduction can be conducted

without an additional solvent. If a solvent is being used then the following solvents are preferred: acetonitrite, ethanol, or aqueous dioxane.

5 Because of the hazardous nature of many of the reducing agents or of the reaction products, the preparation should be conducted in a closed system to avoid exposure to irritating fumes.

10 The condensation of the compounds of the formula R^3L wherein R^3 has the above meanings and L is a leaving group (halogen, mesyloxy, benzenesulfonyloxy, ethanesulfonyloxy or tosyloxy) with a compound of the Formula XIII is carried out under the usual amide alkylating conditions. The amides of Formula XIII are very weak bases. In order to activate the amides, they
15 must first be converted to their anions in order to increase their reactivity. This is effected with strong bases such as sodium, preferably sodium hydride but also alkyl alkali compounds such as butyl lithium, and by adding the alkylating agent R^3L . Because the alkylation involves the release of the acid HL, one usually employs
20 the strong base in stoichiometric excess. The alkylation is generally carried out in an inert solvent at a temperature between 20 and 100°C. The following inert solvents are employed: N, N-dialkylformamides
25 such as N,N-dimethylformamide or tetrahydrofuran. Details of the alkylation are described in Synth. Commun. 9, 757 (1979), Chem. Lett. 1143 (1981), and Synthesis 527, 549 (1979).

30 Alternatively, the alkylation can be carried out by phase-transfer catalysis. The reaction can be carried out in a conventional catalytic two-phase system comprising a concentrated alkali hydroxide solution as the aqueous phase and a non-aqueous phase comprising an inert solvent for the product. The reaction is effected

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with an alkylating agent R^3Br used in 10 to 50% excess added slowly to the system containing a phase-transfer catalyst such as tetra-n-butyl-aminium hydrogen sulfate. The liquid-liquid two-phase system can be replaced with a solid-liquid system comprising powdered alkali hydroxide/alkali carbonate suspended in an inert solvent in the presence of a phase-transfer catalyst such as tetra-n-butylaminium hydrogen sulfate. In both instances the reaction mixture is kept at reflux after addition of the alkylating agent until the reaction is completed. The resultant mixture is cooled to room temperature and the compound of Formula I isolated after separation of the organic phase or by other conventional methods such as extraction. Details of the procedure are described in Synthesis, Communications 1005 (1981).

The amides of Formula XIII are obtained by the formylation method described for step (a) above.

The compounds of Formula I with R^1 hydroxy, nitro, or amino substituents can be converted to other R^1 substituents in a manner known per se. The R^1 nitro group can be converted to an amino group by a number of well-described methods, either the metallic reducing agents such as zinc, tin or iron and acid, catalytic hydrogenation, sulfides such as sodium hydrogensulfide, ammonium sulfide, complexes of aluminum trihydride with aluminum chloride or hydrazine and a catalyst. Specifically useful methods are described by Joffe, Tartakovskii, and Novikov, Russ. Chem. Rev. 35, 19-32 (1966).

The resulting amino compounds in turn can be alkylated or acylated. The alkylation is conducted with alkyl halides, sulfates, such as dimethyl sulfate or sulfonates. The amino compounds can also be acylated in a manner known per se with acyl halides, anhydrides,

esters or with acids. The conditions follow that of the well-known Schotten-Baumann procedure. Frequently aqueous alkali is added to combine with the liberated hydrogen halide. If acids are being used the reaction is made to proceed in good yield at room temperature with dehydrating agents such as dicyclohexylcarbodiimide or N,N'-carbonyl diimidazole. The acylation can also be carried out as anhydrous coupling of the acid chloride with the free base in a suitable organic solvent (toluene, tetrahydrofuran, ethyl acetate) with good mechanical stirring.

The compounds of Formula I with R^1 being alkoxy can also be prepared from the compounds with R^1 being a hydroxy group by alkylation. The reaction proceeds quickly with diazo compounds such as diazomethane under mild conditions with high yields. The best method, however, is the Williamson reaction which is carried out in the presence of a base.

The hydrogenation of the compounds of Formula XIV to the compounds of Formula I can be effected by methods known for the partial hydrogenation of aromatic compounds.

The compounds of Formula XIV are prepared by heating a mixture of an optionally substituted 1,8-naphthalic acid anhydride and an amine of the formula R^3NH_2 in an inert solvent at 80 to 200°C until completion, preferably in the presence of a dehydrating agent such as an anhydride or diimide, followed by reduction of the carbonyl group at the 3-position of the benz[de]isoquinoline-1,3-dione derivative with alkali boranates. The hydrogenation of the compounds of Formula XIV to the compounds of Formula I is effected by methods known to convert naphthalene derivatives to tetralines. The compounds of Formula I with R^1 being hydroxy are prepared by dealkylation or debenzylation of

starting materials of the Formula I with R^1 being either alkyloxy or phenylalkyloxy, in particular benzyloxy.

5 The dealkylation is carried out preferably by acid cleavage of the alkyl aryl ether, preferably with hydrogen iodide or hydrogen bromide. Other suitable
cleaving agents are Lewis acids such BF_3 , BCl_3 , BBr_3 or $AlCl_3$ or anhydrous sulfonic acids or Grignard reagents. If HBr or HI are used the reaction is generally carried
10 out with the acid addition salt of the alkyl aryl ether using an excess of cleaving agent without a solvent at elevated temperatures, i.e., $40^\circ C$ to the boiling point of the reaction mixture, preferably 60 to $95^\circ C$.

The debenzylation is carried out around room temperature under hydrogen with a palladium, platinum or
15 rhodium catalyst with the benzyl aryl ether in solution in an inert solvent. Frequently the catalyst is removed by filtration for recovery and regeneration.

Accordingly, therapeutically active compounds of this invention are especially prepared by

20 (1) reacting an amide of Formula II with a formylating agent in the presence of a strong base to form a compound of Formula IA,

(2) hydrogenating a compound of Formula IA to form a compound of Formula IB,

25 (3) converting an acid addition salt of a compound of Formula I to the corresponding free base,

(4) converting a free base of a compound of Formula I to the corresponding pharmaceutically acceptable salt,

30 (5) oxidizing a compound of Formula I to form the corresponding N-oxide of the R^3 component of Formula I, or

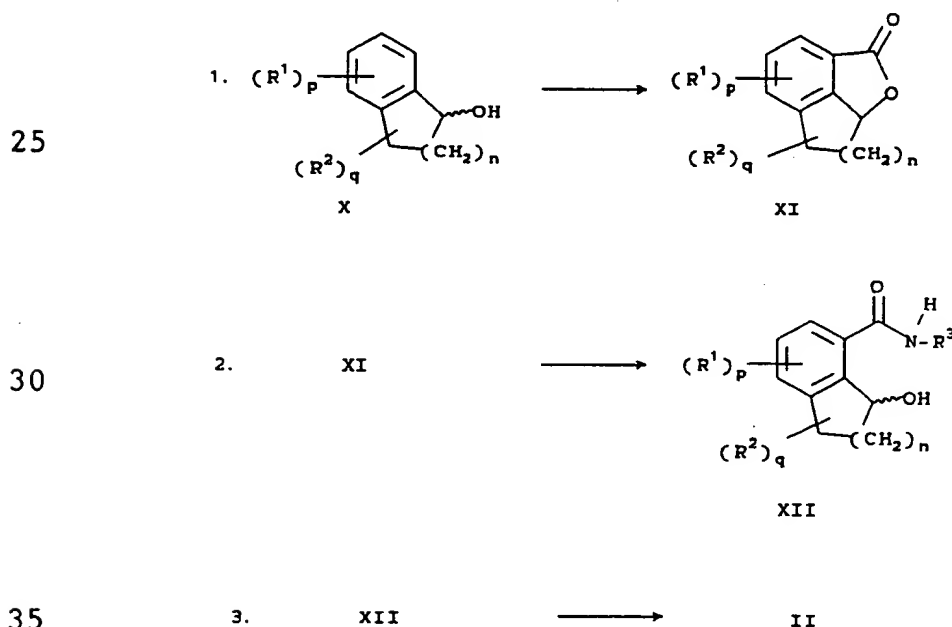
(6) separating a mixture of isomers of a compound of Formula I into a single isomer.

In any of the above last step processes, a reference to Formula I, IA, IB, or II refers to such Formulae wherein n, p, q, R¹, R², R³, R⁴, R⁵, u, x, y, and z are as defined in their broadest definitions set forth in the Summary of the Invention, with the processes applying particularly well to the presently preferred embodiments.

PREPARATION 1

A. This preparation presents a generic description of a method for preparing compounds of Formula II (particularly where q is 0), which compounds are useful as intermediates for the preparation of compounds of Formula I of this invention. In general, the process involves three steps.

REACTION SCHEME II



While this 3-step process may be used to prepare compounds of Formula II (and thus Formula I) where p , n , R^1 and R^3 are broadly defined, it is particularly useful for preparing compounds of Formula II where n is 3 and p is 0.

5 In Step 1, an alcohol of Formula X is reacted with with a strong base such as an alkyllithium (e.g. *n*-butyllithium) at elevated temperatures to form an intermediate anion. The reaction takes place in a
10 suitable, inert organic solvent such as an alkane, e.g. hexane generally at reflux temperature for a period of time sufficient to form the intermediate. Then carbon dioxide is bubbled through to complete the reaction (about 5 hours) and form the lactone of Formula XI.

15 In step 2, the resulting lactone is reacted with an amine of the Formula R^3NH_2 under conditions similar to those discussed hereinbefore regarding amide formation from an ester of Formula III in Reaction Scheme I.

20 In step 3, the resulting hydroxy amide is reduced to form a compound of Formula II under standard reduction (hydrogenation) conditions using a standard reducing catalyst such as 20% palladium hydroxide on carbon.

25 B. 2,6,7,8,9,9a-HEXAHYDROCYCLOHEPT[cd]ISOBENZO-FURAN-2-ONE (A compound of Formula XI wherein $n = 3$ and $p = 0$).

30 (1) To a solution of 5,6,7,8-tetrahydro-9H-benzocyclohepten-9-ol (4.03 g, 31.9 mmol) in hexane (100 ml) heated under reflux was added dropwise during a 5 minute period, a 2.5 molar solution of *n*-butyllithium in hexane (32 ml, 80.0 mmol). After being heated under reflux for 20 hours, the stirred mixture was cooled to
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10°C and dry carbon dioxide was bubbled through for 5 h, during which time a white precipitate separated. The reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate. The aqueous solution was adjusted to pH 2.0 with concentrated hydrochloric acid while being stirred in an ice-water bath. The resulting precipitate was filtered and recrystallized from hexane to afford 2,6,7,8,9,9a-hexahydrocyclohept[cd]isobenzofuran-2-one (2.63 g), m.p. 84-85°C.

(2)-(3) For a further exemplification of these steps see Example 3.

EXAMPLE 1

PREPARATION OF COMPOUNDS OF FORMULA II WHEREIN n IS 1.

A. N-(1-AZABICYCLO[2.2.2]OCT-3-YL)-4-INDAN-CARBOXAMIDE (A compound of Formula II wherein n = 1, p = q = 0, and R³ = 1-azabicyclo[2.2.2]oct-3-yl)

From ethyl 4-indancarboxylate (Formula III wherein X = OC₂H₅; Reaction Scheme I, Step 1)

(1) A solution of (RS)-3-amino-1-azabicyclo[2.2.2]octane (1.51 g, 12 mmol) in toluene (20 ml) was added dropwise to a stirred solution of trimethylaluminum (12 mmol) in toluene (6 ml), so that the temperature did not exceed 10°C. The mixture was stirred for 30 minutes, and a solution of ethyl 4-indancarboxylate (2.16 g, 11.3 mmol) in toluene (20 ml) was gradually added. The reaction mixture was heated under reflux for 16 hours, then cooled to room temperature. The reaction mixture was added at 0° C to aqueous hydrochloric acid (10%, 20 ml). After separation

of the layers, the aqueous layer was made basic with 10 N aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was dried with anhydrous potassium carbonate, filtered and evaporated to afford 2.42 g (79%) of a white solid. A sample recrystallized from ethyl acetate gave (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indancarboxamide, m.p. 158-158.5°C. Anal.: Calcd. for C₁₇H₂₂N₂O: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.95; H, 8.22; N, 10.50.

(2) By following the above procedure of Part A(1), but substituting (S)- or (R)-3-amino-1-azabicyclo[2.2.2]octane for the (RS) mixture, one obtains (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indancarboxamide (60% yield), m.p. 159-160°C; $[\alpha]_D^{25}$ -47.5° (c 0.4, CHCl₃), or (R)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indancarboxamide.

B. Other 4-indancarboxamides of Formula II where n is 1 and R³ is another substituent.

By following the procedure of part A(1) of this example but changing (RS)-3-amino-1-azabicyclo[2.2.2]octane to 4-amino-1-azabicyclo[2.2.2]octane; endo-3-amino-9-methyl-9-azabicyclo[3.3.1]nonane; endo-3-amino-8-methyl-8-azabicyclo[3.2.1]octane; exo-3-amino-8-methyl-8-azabicyclo[3.2.1]octane; or endo-4-amino-1-azabicyclo[3.3.1]nonane; the following compounds of Formula (II) are respectively prepared: N-(1-azabicyclo[2.2.2]oct-4-yl)-4-indancarboxamide; N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-4-indancarboxamide;

N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-indan-
carboxamide;

N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-indan-
carboxamide; or

5 *N*-(endo-1-azabicyclo[3.3.1]non-4-yl)-4-indancarboxamide.

C. 5-Methoxy-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-
indancarboxamide.

10 By following the procedure of Part A(1) or A(2) of
this Example, but substituting ethyl 5-methoxy-4-indan-
carboxylate for ethyl 4-indancarboxylate, one obtains
(*RS*)-5-methoxy-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-4-indan-
carboxamide or the respective (*S*)- or (*R*)-isomer.

15

EXAMPLE 2

PREPARATION OF COMPOUNDS OF FORMULA II WHERE *n* IS 2.

A. (*S*)-*N*-(1-AZABICYCLO[2.2.2]OCT-3-YL)-
20 5,6,7,8-TETRAHYDRO-1-NAPHTHALENECARBOXAMIDE (A compound
of Formula II wherein *n* = 2, *p* = *q* = 0 and
*R*³ = (*S*)-1-azabicyclo[2.2.2]oct-3-yl)

25 From 5,6,7,8-tetrahydro-1-naphthalene-
carboxylic acid. (Formula III wherein *X* = OH, Reaction
Scheme I, Step 1)

A solution of 5,6,7,8-tetrahydro-1-naphthalene-
carboxylic acid (Ofosu-Asante, K. and Stock, L.M.,
30 J. Org. Chem. 1986; 51: 5452) (2.06 g, 11.7 mmol),
oxalyl chloride (1 ml, 11.7 mmol), and dimethylformamide
(0.1 ml) in dichloromethane (20 ml) was stirred at room
temperature for one hour. The mixture was then
concentrated under reduced pressure, and the residue was

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dissolved in dichloromethane (20 ml). The resulting solution was added dropwise at 0°C to a solution of (S)-3-amino-1-azabicyclo[2.2.2]octane (1.48 g, 11.7 mmol) in dichloromethane (20 ml). The solution was stirred at room temperature for 30 minutes, and the solvent was evaporated under vacuum. The residue was dissolved in water and washed with ethyl acetate. The aqueous layer was basified with NH₄OH and extracted with dichloromethane. The dichloromethane was dried with anhydrous potassium carbonate, filtered and then evaporated to afford 2.75 g of white crystals. A sample recrystallized from ethyl acetate/hexane gave (S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, m.p. 159-160°C; $[\alpha]_D^{25}$ -42.1° (c 0.65, CHCl₃).

B. Other 5,6,7,8-tetrahydro-1-naphthalene-carboxamides of Formula II where n is 2 and R³ is another substituent.

By following the procedure of Part A of this Example 2, but changing (S)-3-amino-1-azabicyclo[2.2.2]octane to 4-amino-1-azabicyclo[2.2.2]octane; endo-3-amino-9-methyl-9-azabicyclo[3.3.1]nonane; endo-3-amino-8-methyl-8-azabicyclo[3.2.1]octane; exo-3-amino-8-methyl-8-azabicyclo[3.2.1]octane; or endo-4-amino-1-azabicyclo[3.3.1]nonane; the following compounds of Formula (II) are respectively prepared: N-(1-azabicyclo[2.2.2]oct-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide; N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-
5,6,7,8-tetrahydro-1-naphthalene carboxamide;
N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-
5,6,7,8-tetrahydro-1-naphthalenecarboxamide; or
5 *N*-(endo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-
1-naphthalenecarboxamide.

C. 2-Methoxy-, 4-methoxy-, and 4-benzyloxy-
N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-
10 1-naphthalenecarboxamide.

By following the procedure of Part A of this
Example 2, but substituting 2-methoxy-5,6,7,8-tetrahydro-
1-naphthalenecarboxylic acid for 5,6,7,8-tetrahydro-
15 1-naphthalenecarboxylic acid, one obtains
(*S*)-2-methoxy-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-
5,6,7,8-tetrahydro-1-naphthalenecarboxamide,
m.p. 270-271°C, its 4-methoxy-isomer and
(*S*)-4-benzyloxy-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-
20 5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

D. 4-Chloro-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-
5,6,7,8-tetrahydro-1-naphthalenecarboxamide.

By following the procedure of Part A of this
Example 2, but substituting 4-chloro-5,6,7,8-tetrahydro-
1-naphthalenecarboxylic acid for 5,6,7,8-tetrahydro-
1-naphthalenecarboxylic acid, one obtains
(*S*)-4-chloro-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-
25 5,6,7,8-tetrahydro-1-naphthalenecarboxamide.
30

E. *N*-(ENDO-9-METHYL-9-AZABICYCLO[3.3.1]NON-3-YL)-
5,6,7,8-TETRAHYDRO-1-NAPHTHALENECARBOXAMIDE (A compound
35

of Formula II wherein $n = 2$, $p = q = 0$ and
 $R^3 = \text{endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl}$

5 A solution of 5,6,7,8-tetrahydro-1-naphthalene-
carboxylic acid (571 mg, 3.24 mmol), oxalyl chloride
(0.44 ml, 5.0 mmol), and dimethylformamide (0.05 ml) in
dichloromethane (20 ml) was stirred at room temperature
for one hour. The mixture was then concentrated under
reduced pressure and the residue was dissolved in toluene
10 (10 ml). The resulting solution was added dropwise to a
stirred mixture of *endo*-3-amino-9-methyl-9-aza-
bicyclo[3.3.1]nonane (500 mg, 3.24 mmol) and sodium
carbonate (700 mg, 6.5 mmol) in 5 ml water and 25 ml
toluene. After 2 hours the mixture was diluted with
15 ethyl acetate (100 ml). The layers were separated and
the organic layer was dried with anhydrous magnesium
sulfate, filtered, and concentrated under reduced
pressure to afford 700 mg of white crystals. A sample
recrystallized from ethyl acetate gave *N*-(*endo*-9-methyl-
20 9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-
1-naphthalenecarboxamide, m.p. 166-167°C.

EXAMPLE 3

PREPARATION OF COMPOUNDS OF FORMULA II WHERE n IS 3.

25 A. (RS)-*N*-(1-AZABICYCLO[2.2.2]OCT-3-YL)-
5,6,7,8-TETRAHYDRO-9*H*-BENZOCYCLOHEPTEN-1-CARBOXAMIDE
(A compound of Formula II wherein $n = 3$, $p = q = 0$, and
 $R^3 = 1\text{-azabicyclo[2.2.2]oct-3-yl}$; Reaction Scheme II,
30 Steps 2-3)

A solution of (RS)-3-amino-1-aza-
bicyclo[2.2.2]octane (1.00 g, 8 mmol) in toluene (20 ml)
was added dropwise to a stirred solution of

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trimethylaluminum (8 mmol) in toluene (10 ml), so that the temperature did not exceed 10°C. The mixture was stirred for 30 minutes, and a solution of 2,6,7,8,9,9a-hexahydrocyclohept[cd]isobenzofuran-2-one (Preparation 1B) (1.25 g, 6.6 mmol) in toluene (10 ml) was gradually added. The reaction mixture was heated under reflux 0.5 hours and then cooled to ambient temperature. Water was added gradually until a solid was precipitated, and the mixture was filtered. The solid was washed with ethyl acetate and the combined organic layer was evaporated to afford (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-9H-9-hydroxy-5,6,7,8-tetrahydrobenzocyclohepten-1-carboxamide (1.42 g, 68% yield). Crystallization from ethanolic hydrochloric acid afforded the hydrochloride salt, m.p. 239°C.

Reduction of (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-9H-9-hydroxy-5,6,7,8-tetrahydrobenzocyclohepten-1-carboxamide (1.42 g, 4.5 mmol) in ethanolic hydrochloric acid (20 ml) with 20% palladium hydroxide on carbon (0.5 g) was carried out at 50 psi for 24 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. Purification of the product by column chromatography (10% methanol in methylene chloride and 1% ammonium hydroxide) afforded (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-9H-benzocyclohepten-1-carboxamide (0.52 g, 39% yield).

B. Other compounds of Formula II where n is 3 and R³ is another substituent.

By following the procedure of Part A of this Example 3 but changing (RS)-3-amino-1-azabicyclo[2.2.2]octane to 4-amino-1-azabicyclo[2.2.2]octane,

endo-3-amino-9-methyl-9-azabicyclo[3.3.1]nonane,
endo-3-amino-8-methyl-8-azabicyclo[3.2.1]octane,
exo-3-amino-8-methyl-8-azabicyclo[3.2.1]octane, or
endo-4-amino-1-azabicyclo[3.3.1]nonane,
the following compounds of Formula (II) are respectively
5 prepared:
N-(1-azabicyclo[2.2.2]oct-4-yl)-5,6,7,8-tetrahydro-
9H-benzocyclohepten-1-carboxamide;
N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-
10 5,6,7,8-tetrahydro-9H-benzocyclohepten-1-carboxamide;
N-(endo-8-methyl-9-azabicyclo[3.2.1]oct-3-yl)-
5,6,7,8-tetrahydro-9H-benzocyclohepten-1-carboxamide;
N-(exo-8-methyl-9-azabicyclo[3.2.1]oct-3-yl)-
5,6,7,8-tetrahydro-9H-benzocyclohepten-1-carboxamide; or
15 N-(endo-1-azabicyclo[3.3.1]oct-3-yl)-5,6,7,8-tetrahydro-
9H-benzocyclohepten-1-carboxamide.

EXAMPLE 4

20 PREPARATION OF COMPOUNDS OF FORMULA I WHERE n IS 1
AND THE DASHED LINE IS A BOND.

A. 2-(1-AZABICYCLO[2.2.2]OCT-3-yl)-1,2,4,5-
TETRAHYDROCYCLOPENT[de]ISOQUINOLIN-1-ONE (A compound of
Formula IA wherein n = 1, p = q = 0, and
25 R³ = 1-azabicyclo[2.2.2]oct-3-yl; Reaction Scheme I,
Step 2)

(1) A solution of (RS)-N-(1-azabicyclo[2.2.2]oct-
3-yl)-4-indancarboxamide (Example 1) (2.07 g, 7.7 mmol)
30 in dry tetrahydrofuran (100 ml) at -70°C was treated with
n-butyllithium (20 mmol). The reaction mixture was
stirred at -10°C for one hour, cooled to -70°C, and
dimethylformamide (15 mmol) added in one portion. The
reaction mixture was allowed to warm to room temperature

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over 1.5 hours, then cooled to 0°C and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with 10 N aqueous sodium hydroxide and extracted with ethyl acetate. The ethylacetate was dried over anhydrous sodium sulfate, filtered, and evaporated to afford 1.75 g (81% yield) of white crystals. A sample recrystallized from ethyl acetate gave (RS)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one (Compound A), m.p. 146-147°C. Anal.: Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99%. Found: C, 76.93; H, 7.23; N, 9.90%.

The hydrochloride salt monoethanol adduct [Compound A (HCl)] was prepared from ethanol-HCl: m.p. 188-190°C. Anal.: Calcd. for $C_{18}H_{20}N_2O \cdot HCl \cdot C_2H_5OH$: C, 66.19; H, 7.50; N, 7.72%. Found: C, 66.08; H, 7.55; N, 7.66%.

(2) By following the above procedure but substituting the (S)-isomer of N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-indancarboxamide for the (RS)-mixture, one obtains (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one (Compound B) (50% yield). A sample recrystallized from ethyl acetate had a m.p. 155.5-156°C; $[\alpha]_D^{25} +47.1^\circ$ (c 0.41, $CHCl_3$). Anal.: Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19, N, 9.99%. Found: C, 77.45; H, 7.12; N, 9.84%.

The hydrochloric acid salt [Compound B (HCl)] was prepared from ethanol-HCl: m.p. >285°C; $[\alpha]_D^{25} -12.8^\circ$; Anal.: Calcd. for $C_{18}H_{20}N_2O \cdot HCl \cdot 0.5 H_2O$: C, 66.35; H, 6.81; N, 8.59%. Found: C, 65.96; H, 6.86; N, 8.33%.

(R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-
1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one is
similarly prepared as the hydrochloride [Compound W
(HCl)]: m.p. >285°C; $[\alpha]^{25}_D + 17.1$ (H₂O, C 0.6).

5

B. Other 1,2,4,5-tetrahydrocyclopent[de]iso-
quinolin-1-ones of Formula II where n is 1 and R³ is
another substituent.

10

By following the procedure of Part A(1) of this
Example 4, but substituting other compounds of Example 1B
and 1C for
(RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-indancarboxamide,
one obtains the corresponding compounds of Formula I.

15

EXAMPLE 5

PREPARATION OF COMPOUNDS OF FORMULA I WHERE n IS 2
AND THE DASHED LINE IS A BOND.

20

A. (S)-2-(1-AZABICYCLO[2.2.2]OCT-3-YL)-
2,4,5,6-TETRAHYDRO-1H-BENZ[de]ISOQUINOLIN-1-ONE
(A compound of Formula IA wherein n = 2, p = q = 0, and
R³ = 1-azabicyclo[2.2.2]oct-3-yl; Reaction Scheme I,
Step 2)

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A solution of n-butyllithium in hexane (60 mmol)
was added dropwise at -70°C to a solution of
(S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-
1-naphthalenecarboxamide (Preparation 1) (7.70 g,
21 mmol) in dry tetrahydrofuran (400 ml). The reaction
mixture was stirred at -10°C for one hour, cooled to
-70°C, and dimethylformamide (100 mmol) added in one
portion. The reaction mixture was allowed to warm to
room temperature over 1.5 hours, then cooled to 0°C and
acidified with 10% aqueous hydrochloric acid. The layers

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were separated, and the aqueous layer was washed with ethyl acetate, then made basic with 10 N aqueous sodium hydroxide and extracted with ethyl acetate. The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and evaporated to afford 7.58 g (95% yield) of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one (Compound C) as white crystals; m.p. 117-118°C; $[\alpha]_D^{25} +43.2^\circ$ (c 0.98, CHCl₃).

Crystallization from ethanolic hydrochloric acid afforded 9.75 g of the hydrochloride salt monoethanol adduct [Compound C (HCl)] as white crystals, m.p. >270°C, $[\alpha]_D^{25} -8.4^\circ$ (c 2.4, H₂O). Anal.: Calcd. for C₁₉H₂₂N₂O·HCl·C₂H₅OH: C, 66.91; H, 7.75; N, 7.43%. Found: C, 66.77; H, 7.65; N, 7.27%.

Crystallization from isopropanolic HCl provided the unsolvated hydrochloride salt.

Similarly prepared was (RS)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one; m.p. [HCl salt; Compound D (HCl)] 176-177°C.

Similarly prepared was (R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one; m.p. >275°C; $[\alpha]_D^{25}$ (HCl salt) [Compound E (HCl)] +6.8° (c 2, H₂O).

B. 2-(ENDO-9-METHYL-9-AZABICYCLO[3.3.1]NON-3-YL)-2,4,5,6-TETRAHYDRO-1H-BENZ[de]ISOQUINOLIN-1-ONE (A compound of Formula IA wherein n = 2, p = q = 0 and R³ = endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl; Reaction Scheme I, Step 2)

(1) A solution of n-butyllithium in hexane (5 mmol) was added dropwise at -70°C to a solution of 2-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-

5,6,7,8-tetrahydro-1-naphthalenecarboxamide (Example 2B) (0.7 g, 2.24 mmol) in dry tetrahydrofuran (25 ml).

The reaction mixture was stirred at -10°C for one hour, cooled to -70°C, and dimethylformamide (13 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature over 1.5 hours, then cooled to 0°C and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with concentrated ammonium hydroxide and extracted with ethyl acetate (100 ml). The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and evaporated to afford 2-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinoline-1-one.

The hydrochloride salt [Compound F (HCl)] was prepared from ethanolic HCl; m.p. 236°C. Anal.: Calcd. for $C_{21}H_{27}ClN_2O \cdot H_2O$: C, 66.92; H, 7.75; N, 7.43%. Found: C 66.45; H, 7.79; N, 7.32%.

(2) By following this procedure but substituting other 1-naphthalenecarboxamides of Example 2B for 2-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide, the following compounds are prepared:

2-(1-azabicyclo[2.2.2]oct-4-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one, m.p. [HCl salt; Compound G (HCl)] 335-337°C; 2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one; m.p. [HCl salt; Compound H (HCl)] 269-270°; 2-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one; m.p. [HCl salt; Compound I (HCl)] >270°C; and 2-(endo-1-azabicyclo[3.3.1]non-4-yl)-2,4,5,6-tetrahydro-

1*H*-benz[de]isoquinolin-1-one; m.p. [HCl salt; Compound J
(HCl)] >360°C.

5 C. (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-9-methoxy-
2,4,5,6-tetrahydro-1*H*-benz[de]isoquinolin-1-one.

By following the procedure of Part A
of this Example 5, but substituting the compound
prepared in Example 2C, one obtains
10 (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-9-methoxy-
2,4,5,6-tetrahydro-1*H*-benz[de]isoquinolin-1-one.

D. (S)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-7-chloro-
2,4,5,6-tetrahydro-1*H*-benz[de]isoquinolin-1-one.

15 By following the procedure of Part A of this
Example 5, but substituting the compound prepared in
Example 2D, one obtains
(S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-7-chloro-
20 2,4,5,6-tetrahydro-1*H*-benz[de]isoquinolin-1-one.

EXAMPLE 6

PREPARATION OF COMPOUNDS OF FORMULA I WHERE *n* IS 3
AND THE DASHED LINE REPRESENTS A BOND.

25 A. (RS)-2-(1-AZABICYCLO[2.2.2]OCT-3-YL)-
1,2,4,5,6,7-HEXAHYDROCYCLOHEPT[de]ISOQUINOLIN-1-ONE
(A compound of Formula IA wherein *n* = 3, *p* = *q* = 0 and *R*³
= 1-azabicyclo[2.2.2]oct-3-yl; Reaction Scheme I, Step 2)

30 A solution of *n*-butyllithium in hexane (2.7 mmol)
was added dropwise at -70°C to a solution of
(RS)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-

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9H-benzocycloheptene-1-carboxamide (Example 3A) (0.37 g, 1.2 mmol) in dry tetrahydrofuran (10 ml). The reaction mixture was stirred at -10°C for one hour, cooled to -70°C, and dimethylformamide (1.5 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature over 1.5 hours, then cooled to 0°C and acidified with 10% aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ethyl acetate, then made basic with aqueous ammonium hydroxide. The ethyl acetate was dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated to afford 0.15 g (40% yield) of (RS)-2-(1-azabicyclo-[2.2.2]oct-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one as a foam. The hydrochloride salt [Compound K (HCl)] was prepared from ethanol-HCl; m.p. >285°C.

B. Other compounds of Formula I where n is 3 and R³ is another substituent.

By following the procedure of Part A of this Example 6, but changing (RS)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5,6,7,8-tetrahydro-9H-benzocycloheptene-1-carboxamide to:
N-(1-azabicyclo[2.2.2]oct-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;
N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;
N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;
N-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide; or
N-(endo-1-azabicyclo[3.3.1]non-4-yl)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide;

one obtains the following compounds:

2-(1-azabicyclo[2.2.2]oct-4-yl))-1,2,4,5,6,7-hexahydro-
cyclohept[de]isoquinolin-1-one;

2-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-

5 1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one;

2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-

1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one;

2-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-

1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one; or

10 2-(endo-1-azabicyclo[3.3.1]non-3-yl)-

1,2,4,5,6,7-hexahydrocyclohept[de]isoquinolin-1-one.

EXAMPLE 7

PREPARATION OF COMPOUNDS OF FORMULA I WHERE n IS 1,

15 2 OR 3 AND THE DASHED LINE REPRESENTS 2 HYDROGEN ATOMS.

A. (S)-2-(1-AZABICYCLO[2.2.2]OCT-3-YL)-

2,3,3a,4,5,6-HEXAHYDRO-1H-BENZ[de]ISOQUINOLIN-1-ONE

20 (A compound of Formula IB wherein n = 2, p = q = 0 and R³
= 1-azabicyclo[2.2.2]oct-3-yl; Reaction Scheme I, Step 3)

The reduction of 0.32g (1.1 mmol) of the free base
of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-
tetrahydrobenz[de]isoquinolin-1-one (Compound C of
25 Example 5A) in acetic acid (5 ml) and 3 drops of 70%
perchloric acid with 20% palladium hydroxide on carbon
(0.1 g) was carried out at 85°C and 50 psi for 24 hours.
The catalyst was removed by filtration and the filtrate
was concentrated under reduced pressure. The residue was
30 dissolved in water (10 ml), basified with ammonium
hydroxide solution, and extracted with ethyl acetate.
The ethyl acetate was dried with anhydrous potassium
carbonate, filtered, and evaporated to afford a

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diastereomeric mixture of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one (0.18 g) as a semisolid. Crystallization from a mixture of ethanolic hydrochloric acid, isopropanol, and ether afforded 0.8 g of the hydrochloride salt [Compound L (HCl)] as white crystals; m.p. >270°C. Anal.: Calcd. for $C_{19}H_{14}N_2O \cdot HCl \cdot 0.25 H_2O$: C, 67.64; H, 7.62; N, 8.30%. Found: C, 67.38; H, 7.70; N, 8.10%.

B. By substituting other compounds prepared in Examples 4, 5 and 6 for (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydrobenz[de]isoquinolin-1-one, other compounds of Formula I where n is 1, 2 or 3 and the dashed line represents 2 hydrogen atoms are obtained.

C. A solution of 19.7 g (59.5 mmol) of the hydrochloride salt of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one in 250 ml of acetic acid containing 2 g of 20% Pd(OH)₂ was hydrogenated at 60 psi and 80-85°C for 20 hours. The mixture was filtered and evaporated. The residue was partitioned between aqueous ammonia and dichloromethane and the organic layer was dried (Na₂SO₄) and evaporated. The crude free base mixture was dissolved in 100 ml of ethanol, acidified with ethanolic hydrochloric acid, and treated with ether to precipitate the HCl salts of (3aS,3'S)-2-(1-azabicyclo[2.2.2]-oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one and the (3aR,3'S)-diastereomer. Two recrystallizations from ethanol afforded the pure HCl salt [Compound M (HCl)] of the (3aS,3'S)-diastereomer, m.p. 296-297°C, $[\alpha]_D -98$ (c 0.5 H₂O), yield 6 grams). The free base (Compound M) has a m.p. of 87-88°C, $[\alpha]_D -136^\circ C$ (c 0.25 chloroform).

The mother liquors from the above crystallizations were combined and chromatographed on silica gel (10% methanol-dichloromethane, 1% ammonia to give an enriched fraction of the [3aR,3'S]-diastereomer.

5 Crystallization from ethyl acetate-hexane gave pure [3aR,3'S]-diastereomer base which was converted to the HCl salt [Compound N (HCl)] from ethanoether, m.p. 270-272°C; $[\alpha]_D + 73$ (c 0.2, H₂O).

10 D. In an analogous manner, following the hydrogenation procedure of Section C, the HCl salts of the (3aR,3'R)-diastereomer [Compound O (HCl)] with a m.p. >280°C, $[\alpha]_D + 95^\circ$ (c 0.2 H₂O) and of the (3aS,3'R)-diastereomer [Compound P (HCl)] with a m.p. 15 275-276°C, $[\alpha]_D - 68^\circ$ (c 0.3, H₂O) can be isolated.

E. Using 10% Pd on carbon and Pearlman's catalyst Compound C of Example 5A is hydrogenated in tetrahydrofuran to give Compounds M (m.p. of HCl salt > 20 295°C) and N (m.p. of HCl salt 272°C) in a ratio of about 3:2. Using 10% Pd on carbon Compound C is hydrogenated as the (+) or (-) camphorsulfonic acid salt in ethyl acetate to Compounds L and M in a ratio of about 1:3. Using 10% Pd on carbon Compound C is hydrogenated as the 25 acetate in ethyl acetate to Compounds L and M in a ratio of about 0.85:1. Using 10% Pd on carbon with 61.9% water (Degussa) Compound C is hydrogenated as the free base in toluene to Compounds L and M in a ratio of 2.1:1. Using 5% Pd/BaSO₄ Compound C is hydrogenated in ethyl acetate 30 to Compounds L and M in a ratio of 2.7:1.

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EXAMPLE 8

5 A. (S)-2-(1-AZABICYCLO[2.2.2]OCT-3-YL)-
2,4,5,6-TETRAHYDROBENZ[de]ISOQUINOLIN-1-ONE HYDROCHLORIDE
(A compound of Formula I as a pharmaceutically acceptable
acid addition salt)

10 (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-
2,4,5,6-tetrahydrobenz[de]isoquinolin-1-one is
recrystallized from *n*-propanol/hydrochloric acid to form
the corresponding hydrochloride salt.

15 B. Other hydrochloride salts of the free base
compounds of Examples 1-7 are similarly prepared.

EXAMPLE 9

20 A. (S)-2-(1-AZABICYCLO[2.2.2]OCT-3-YL)-
2,4,5,6-TETRAHYDROBENZ[de]ISOQUINOLIN-1-ONE (A compound
of Formula I as a free base)

25 (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-
2,4,5,6-tetrahydrobenz[de]isoquinolin-1-one hydrochloride
is treated with a molar excess of ethanolic potassium
hydroxide to form the corresponding free base
(Compound C), m.p. 117-118°C.

30 B. Other free base compounds are similarly
obtained from the corresponding acid addition salts of
the compounds prepared in Example 1-8.

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EXAMPLE 10

(S)-2-(1-AZABICYCLO[2.2.2]OCT-3-YL)-
2,4,5,6-TETRAHYDRO-1H-BENZ[de]ISOQUINOLIN-1-ONE N-OXIDE
(A compound of Formula I as the N-oxide)

m-Chloroperoxybenzoic acid (0.82g, 4.7 mmol) was
added in small portions at 0°C to a solution of
(S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-
1H-benz[de]isoquinolin-1-one (Example 5A) (1.16 g,
3.9 mmol) in dichloromethane (50 ml). The reaction
mixture was stirred for additional 0.5 hour at 0°C. The
solvent was removed under reduced pressure and the
residue was purified by column chromatography (10%
methanol in dichloromethane and 1% ammonium hydroxide) to
give the N-oxide of (S)-2-(1-azabicyclo-[2.2.2]oct-3-yl)-
2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one
(Compound Q) (0.75 g; 62% yield) as an amorphous solid;
m.p. 73-75°C.

Other N-oxides of this invention are prepared by
substituting other compounds of Examples 4-6 into the
above procedure.

EXAMPLE 11

5-HT₃ RECEPTOR SCREENING ASSAY

This example describes an *in vitro* assay for
determining the 5-HT₃ receptor affinity of the compounds
of this invention. The method is essentially the method
described by Kilpatrick et al., previously cited, which
measures the affinity of a compound for the 5-HT₃
receptor of the rat cerebral cortex. Compounds of this
invention are screened for affinity at the 5-HT₃ receptor
of rat cerebral cortex radiolabelled with [³H]quipazine.

Membranes are prepared from the cerebral cortices of rat brains homogenized in 50 mM Tris buffer (pH 7.4 at 4°C) using a Polytron P10 tissue disrupter (setting 10, 2 x 10 sec bursts). The homogenate is centrifuged at 48,000 x g for 12 min and the pellet obtained is washed, by resuspension and centrifugation, three times in homogenizing buffer. The tissue pellets are resuspended in the assay buffer, and are stored under liquid nitrogen until required.

The binding assays are conducted using a Tris-Krebs assay buffer of the following composition (mM): NaCl, 154; KCl, 5.4; KH₂PO₄, 1.2; CaCl₂.2H₂O, 2.5; MgCl₂, 1.0; glucose, 11; Tris, 10. Assays are conducted at 25°C at 7.4 in a final volume of 0.25. Zacopride (1.0 µM) is used to define the non-specific binding (NSB). 5HT₃ receptors present in rat cortical membranes are labelled using 0.3-0.7 nM [³H]quipazine (specific activity 50-66 Ci/mmol; New England Nuclear) in the presence of 0.1 µM paroxetine to prevent [³H]quipazine binding to 5-HT uptake sites. The rat cortex membranes are incubated with [³H]quipazine in the presence of 10 different concentrations of compound to be tested at concentrations ranging from 1x10⁻¹² to 1x10⁻⁴ molar. Incubations are conducted for 45 min at 25°C and are terminated by vacuum filtration over Whatman GF/B glass fiber filters using a Brandel 48 well cell harvester. After filtration the filters are washed for 8 sec with 0.1 M NaCl. The filters are pretreated with 0.3% polyethyleneimine 18 hr prior to use in order to reduce filter binding of the radioligand. Radioactivity retained on the filters is determined by liquid scintillation counting.

The concentration of compound producing 50% inhibition of radioligand binding is determined by use of

an iterative curve fitting procedure. Affinities are expressed as the negative logarithm of the IC_{50} value (pIC_{50}). Compounds of this invention exhibit pIC_{50} values showing 5-HT₃ receptor antagonist affinity, e.g. values greater than 6.

EXAMPLE 12

GASTRIC EMPTYING OF TEST MEAL IN RATS

This Example describes an *in vivo* method of determining the gastrointestinal activity of the compounds of the invention. The method is the method described by Droppleman et al., previously cited, which measures gastric emptying of test meal in rats.

The following formulation is used as the test meal administered to the rats. Twenty g of cellulose gum (Hercules Inc., Wilmington, Delaware) is slowly added to 200 ml of cold distilled water while being mixed in a Waring blender at approximately 20,000 rpm. Mixture of the cellulose gum continues (approximately 5 min) until complete dispersion and hydration of the cellulose gum has taken place. Three beef bouillon cubes are dissolved in 100 ml of warm water and then blended into the cellulose solution followed by 16 g of purified casein (Sigma Chemical Co., St. Louis, MO), 8 g of powdered confectioners sugar, 8 g of cornstarch, and 1 g of powdered charcoal. Each ingredient is added slowly and mixed thoroughly resulting in approximately 325 ml of a dark gray to black, homogenous paste. The meal was then refrigerated overnight to allow for trapped air to escape. Prior to the assay the meal is removed from the refrigerator to allow it to warm to room temperature. Once to room temperature, 3 ml of meal is filled into 5 ml disposable syringes for oral dosing of animals, with

each animal requiring one filled syringe. Five test meal samples are weighed on an analytical balance and these weights were averaged to find a mean test meal weight that is later used in the calculations of meal emptied.

5 Mature (170 to 204 g) male Sprague-Dawley rats are deprived of food for 24 hrs with water ad libitum. On the morning of the study each animal is weighed and randomly assigned to treatment groups consisting of ten animals per group. Starting at 0 hr each animal receives
10 either control, test, or reference substance (metoclopramide) by intraperitoneal injection. At time 0.5 hr each animal is orally dosed with 3 ml of test meal. At time 1.5 hr each animal is sacrificed by carbon dioxide inhalation. The stomach is removed by opening
15 each animal's abdomen and carefully clamping and cutting the esophagus and cutting just below the pyloric sphincter of the stomach. Each stomach is placed, taking care not to lose any of the stomach contents, on a small, previously weighed and correspondingly labeled 7 ml weigh
20 boat and immediately weighed on an analytical balance. Following weighing each stomach is cut open along the lesser curvature of the stomach and was rinsed with tap water and gently blotted dry to remove excess moisture. After reweighing the empty stomach, the difference
25 between the weight of the full stomach and the empty stomach minus the weigh boat weight indicates the amount of of test meal remaining in the stomach, and this value is subtracted from the average weight of 3 ml of test meal to yield the quantity of test meal emptied during
30 the 1.5 hour post injection time period. The mean and standard deviation amount of meal emptied by test and reference groups are compared to the mean and standard deviation of meal emptied by the control group by use of Dunnett's t-test (Statistical Association Journal,

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December 1955, 1096-1121). Per cent difference from control is also calculated for the treatment groups.

The compounds of this invention when administered intraperitoneally increase gastric emptying of a test meal in rats as shown by the following results:

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<u>Compound</u>	<u>(N)</u>	<u>Mean \pm 50 (gm.)^c</u>	<u>$\Delta\%$^c</u>
control‡	(25)	1.77 \pm 0.20	---
10 N(HCl)	(6)	2.44 \pm 0.18*	22.5
M(HCl)	(10)	2.32 \pm 0.25	16.3
C(HCl)	(10)	2.03 \pm 0.36*	27.2
Q	(9)	2.27 \pm 0.20*	32.7
metoclopramide‡	(29)	2.42 \pm 0.26*	37.3

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- * Significance from control; PL 0.05.
- ‡ Mean results from 3 separate experimental runs.
- c Percentage increase from control is calculated and statistical analysis is performed using controls particular to each experimental run.

EXAMPLE 13

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CISPLATIN-INDUCED EMESIS IN FERRETS

This study shows the effects of compounds of Formula I, given intravenously (iv), on cisplatin-induced emesis in ferrets.

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Adult, male, castrated ferrets are allowed food and water ad libitum both prior to and throughout the testing period. Each animal is randomly chosen and anesthetized with a metofane/oxygen mixture, weighed and assigned to one of three test groups. While anesthetized an incision is made along the ventral cervical region approximately two to four centimeters in length. The jugular vein is then isolated and subsequently cannulated with a capped saline filled PE-50 polyethylene tubing. The cannula is

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exteriorized at the base of the skull and the incision closed with wound clips. The animals are then returned to their cages and allowed to recover from anesthesia before intravenous (iv) administration of either vehicle (1.0 ml/kg) or test compound (1.00 mg/kg). Within 2.0 minutes of the administration of a test compound (iv), an iv dose of cisplatin (10 mg/kg) is given. The animals are then observed for five hrs (post dosing) and emetic responses (i.e., vomiting and/or retching) are recorded. For purposes of this Example and of Example 16, vomiting is defined as the successful evacuation of stomach contents, while a single episode of retching is defined as rapid and successive efforts to vomit (within a one minute time period). At the end of this observation period each animal is euthanised by a lethal barbiturate injection.

Emetic responses are represented as (1) time to onset of emesis, (2) total vomiting episodes and (3) total retching episodes. Means and standard deviations of the test groups are compared to those of the reference groups. Significance is determined by Student's t-test when comparing a single treatment group to the vehicle control or by Dunnett's comparative analysis when more than one treatment group is compared to a single vehicle.

Intravenously administered compounds of Formula I are anti-emetic in this assay as shown by the following results:

	<u>Treatment</u>	Dose, P.O. <u>(mg/kg)</u>	<u>N</u>	Time to <u>Onset</u>	Retching <u>Episodes</u>	Vomiting <u>Episodes</u>
	Vehicle	1.0 ml/kg	5	33.6±6.9	11.0±2.9	14.2±5.5
	N(HCl)	0.1	6	79.7±16.6	3.5±2.3	3.3±2.7
5	Vehicle	1.0 ml/kg	5	33.6±6.9	11.0±2.9	14.2±5.5
	M(HCl)	0.1	5	90.0±21.2	0.8±1.3	0.8±1.3
	Vehicle	1.0 ml/kg	5	54.0±10.9	11.4±4.3	13.2±7.3
	C(HCl)	0.1	6	86.5±2.1	1.0±1.5	0.7±1.0
10	Vehicle	1.0 ml/kg	6	50.0±4.0	11.7±2.3	16.5±5.8
	M(HCl)	0.1	6	76.5±43.6	3.5±3.7	5.3±7.2
	Vehicle	1.0 ml/kg	6		11.8±4.6	12.5±4.5
	V(HBr)	0.1	5		7.4±3.3	6.8±3.4
	Vehicle	1.0 ml/kg	6	37.2±5.0	16.5±2.6	19.5±3.2
	M(HCl)	0.1	6	N/A	0.5±1.2	0±0

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Proceeding as in this Example, but administering the test compounds by oral route, the anti-emetic effects of compounds of Formula I may be evaluated. Orally administered compounds of Formula I are anti-emetic in this assay.

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EXAMPLE 14

5-HT₃ ANTAGONIST ACTIVITY IN RATS (VON BEZOLD-JARISCH REFLEX)

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This Example describes an *in vivo* method for determining the 5-HT₃ antagonist activity of the compounds of the invention. The method is a modified version of the methods described by Butler et al., Cohen et al., and Fozard, all previously cited, which measure 5-HT₃ antagonist in rats; where 2-methyl-5-hydroxytryptamine was used rather than 5-HT itself.

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Male Sprague-Dawley rats, 250-380 g are anesthetized with urethane (1.4 g/kg, ip), and cannulated (trachea, left femoral vein and either duodenum or jugular vein). The heart rate is recorded, using Gould ECG/Biotech amplifiers. After at least 30 min equilibration, each rat is titrated (iv) with 2-methyl-5-hydroxytryptamine (2-m-5HT) and a minimal dose that induced a sufficient and consistent bradycardia is chosen.

For an intravenous dose range (potency) study, the rat is challenged with the selected dose of 2-m-5HT every 12 min. A test compound is administered intravenously in increasing doses 5 min before each injection of 2-m-5HT, until the response to 2-m-5HT is blocked. A separate group of rats receiving vehicle is similarly tested.

For duration studies, a single dose of a test compound or vehicle is injected intravenously or intraduodenally to the rat and the rat is challenged with 2-m-5HT at 5, 15, 30, 60, 120, 180, 240, 300 and, in some studies, 360, 420 and 480 min post dose.

For both potency and duration studies heart rate (beats/min) is recorded continuously for the duration of the study. The peak decrease in heart rate evoked by 2-m-5HT is monitored, using a computer. The change in responses to 2-m-5HT before and after administration of the vehicle or the compound is calculated. This is expressed as percent inhibition from the predose value. Data are analyzed using a one-way repeated measures ANOVA and followed by pairwise comparison to vehicle control using Fisher's LSD strategy. From a dose-response curve so constructed, an ID₅₀ value is obtained to represent the dose that inhibited 50% of the bradycardic effect induced by 2-m-5HT.

Compounds of this invention are active in this assay. Specifically, Compounds C(HCl), M, M(HCl), N(HCl) and R(HCl) are equal in activity to Odansetron or more active than Odansetron (ID50 ~ 3.2 mg/kg).

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EXAMPLE 15

THE ANXIOLYTIC BEHAVIOR MODEL

10 This Example describes an *in vivo* method for determining the CNS activity, i.e. the anxiolytic activity, of compounds of the invention.

15 Naive male C5BI/6J mice, 18-20 g, are kept in groups of 10 mice in quarters controlled for sound, temperature and humidity. Food and water are available *ad libitum*. The mice are kept on a 12 hr light and 12 hr dark cycle, with lights on at 6:00 a.m. and off at 6:00 p.m. All experiments begin after at least 7 days have lapsed after arrival at the site.

20 The automated apparatus used for the detection of changes in exploration was obtained from Omni-Tech Electronics Columbus Ohio and was similar to that of Crawley and Goodwin (1980), as described in Kilfoil et al., cited previously. Briefly, the chamber consisted of a plexiglass box (44 x 21 x 21 cm), divided into two chambers by a black plexiglass partition. The partition
25 dividing the two chambers contained a 13 x 5 cm opening through which the animal could easily pass. The dark chamber (42 cm x 21 cm x 30 cm) has clear sides and a white floor. A fluorescent tube light (40 watt) placed above the chambers provides the only illumination. The
30 Digiscan Animal Activity Monitor System RXYZCM16 (Omni-Tech Electronics) is used to record the exploratory activity of animals within the test chambers.

35 Prior to administration of vehicle (DDH₂O) or

<u>COMPOUND</u>	<u>SHUTTLE</u>		<u>LOCOMOTOR</u>		<u>TIME DARK</u>		<u>LATENCY (SEC)</u>		<u>% ACTIVITY</u>	
	<u>ACTIVITY</u>		<u>(LIGHT AREA)</u>		<u>AREA (SEC)</u>		<u>(SEC)</u>		<u>DARK AREA</u>	<u>2*</u>
	Mean \pm SD	$\Delta\%$	Mean \pm SD	$\Delta\%$	Mean \pm SD	$\Delta\%$	Mean \pm SD	$\Delta\%$	Mean \pm SD	$\Delta\%$
Ondansetron	121.0 \pm 12.4*	7.5	1528 \pm 77.8*	52.6	499.4 \pm 14.8*	-12.8	6.7 \pm 1.5	4.7	78.8 \pm 2.4*	-13.1
E(HCl)	266.5 \pm 43.4*	95.8	1677 \pm 66.9*	34.6	504.8 \pm 13.2*	-9.4	2.6 \pm 0.2	4.0	78.1 \pm 2.3	-7.5
C (HCl)	159.8 \pm 22.8	40.2	1534 \pm 72.9*	41.1	452.4 \pm 17.9*	-20.1	7.6 \pm 0.9	80.9	77.4 \pm 2.7*	-12.3
M (HCl)	59.8 \pm 8.2	31.9	1844 \pm 54.4*	57.6	454.5 \pm 17.4*	-18.2	8.1 \pm 1.2	86.9	71.3 \pm 2.8	-18.1
P (HCl)	148.4 \pm 14.8*	92.7	1696 \pm 112*	33.4	479.0 \pm 12.5*	-12.5	7.6 \pm 1.1	65.2	74.4 \pm 1.9	-14.6

* Significance from control; $p < 0.05$

Percentage change from control ($\Delta\%$) is calculated and statistical analysis is performed using controls particular to each experimental run.

2* Unaltered or decreased % locomotor activity in the dark area is an indication that increased exploratory activity is not the result of an overall increase in locomotor activity but is the reflection of anxiolytic activity.

The two compartment exploratory model of Crawley and Goodwin demonstrates that anxiolytic (antianxiety) compounds of Formula I increase the amount of time spent in the light area, increase the amount of shuttle activity in the light area and either do not affect or increase locomotor activity in the light area.

The above results demonstrate that the compounds of this invention are effective in this assay.

EXAMPLE 16

CISPLATIN-INDUCED EMESIS IN DOGS

The following describes the procedure for determining the intravenous (i.v.) effects of compounds of Formula I on cisplatin-induced emesis in dogs.

Male and female dogs (6-15 kg) are fed one cup of dry dog food. One hour following feeding, cisplatin (cis-diamminedichloroplatinum) is administered i.v. at 3 mg/kg. Sixty minutes after the administration of cisplatin, either vehicle or test compound is injected i.v. at 0.1 ml/kg and 1.0 mg/kg, respectively. The dogs are then observed continuously for a 5 hour period and the emetic responses (i.e., vomiting and/or retching) are recorded.

Emetic responses are represented as (1) time to onset of emesis, (2) total vomiting episodes and (3) total retching episodes. Means and standard deviations of the test groups are compared to those of the reference groups. Significance is determined by Student's t-test when comparing a single treatment group to the vehicle control or by Dunnett's comparative analysis when more than one treatment group is compared to a single vehicle.

Compounds of Formula I exhibit anti-emetic activity in this assay.

EXAMPLE 17

5 The Mouse Light/Dark Withdrawal Anxiety Test

 The following procedure describes a method to determine whether compounds of Formula I affect the anxiety that occurs after abruptly ceasing chronic treatment with drugs of abuse.

10 Naive male BKW mice (25-30 g) are caged in groups of ten in quarters controlled for sound, temperature and humidity. Food and water are available ad libitum. The mice are kept on a 12 hour light cycle and 12 hour dark cycle, with lights on at 6:00 a.m. and off at 6:00 p.m.

15 All experiments begin at least 7 days after arrival on site.

 Anxiolysis is determined by the two-compartment exploratory model of Crawley and Goodwin (see Example 15). Measurements include time spent in the light compartment, locomotion activity (grid crossings/5 min.), rears and latency (the time for the mouse to move to the dark chamber when first placed in the center of the lighted area).

25 Increased exploratory activity in the lighted area is induced by treating the mice for 14 days with alcohol (8.0 % w/v in drinking water), nicotine (0.1 mg/kg, i.p., twice daily) or cocaine (1.0 mg/kg, i.p., twice daily). Anxiolysis is assessed 1, 3, 7 and 14 days after commencement of the drug regime. The treatment is abruptly ceased and exploratory activity in the lighted area is determined 8, 24 and 48 hours thereafter.

30 Vehicle or test compounds are administered during the withdrawal phase by intraperitoneal injection. Activity

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is measured as inhibition of the decrease in anxiolytic behavior after the alcohol, cocaine or nicotine treatment is ceased.

Compounds of Formula I decrease the anxiety associated with drug withdrawal in this model as shown by the following results:

		Time in Dark (%)	Latency (sec.)	Rears/5 Min in Light	Crossings/ 5 Min in Light
10	Control	58.3±5.9	8.0±0.7	22.4± 2.4	24.4± 2.7
	diaz W/D	70.0±8.0*	1.8±0.1*	8.4± 0.9*	7.8± 0.9*
	W/D+C(HCl)°	29.4±3.2*‡	27.8±2.9*‡	97.8±10.7*‡	113.2±13.1*‡
	Control	59.0±6.0	9.6±1.5	26.0± 2.8	33.0± 3.6
	nic W/D	69.7±7.0*	2.0±0.01*	9.6± 1.1*	10.4± 1.4*
	W/D+C(HCl)°	29.0±3.0*‡	19.7±3.5*‡	90.1±10.0*‡	100.0±11.0*‡
15	Control	58.4±6.0	7.3±0.9	28.6± 3.2	37.0± 4.0
	alc W/D	80.0±8.2*	2.0±0.3*	12.3± 1.8*	14.3± 1.7*
	W/D+C(HCl)°	63.7±6.6‡	9.6±1.4‡	73.5±7.6*‡	88.0± 9.1*‡
	Contrl	58.0±5.9	9.8±1.5	30.2± 3.3	34.2± 3.6
	coc W/D	74.5±7.5*	1.8±0.2*	8.6± 1.0*	8.0± 0.9*
20	W/D+C(HCl)°	25.8±2.7*‡	20.0±2.9*‡	91.0±10.2*‡	117.0±13.0*‡

W/D = withdrawal

diaz = diazepam; nic = nicotine; alc = alcohol;

coc = cocaine

* significance from control; $p < 0.01$

‡ significance from W/D; $p < 0.01$

° 1 µ/g/kg of C(HCl) is administered i.p.

EXAMPLE 18

THE MOUSE HABITUATION/COGNITIVE ENHANCEMENT TEST

The following describes a model to determine the cognitive enhancing effects of compounds of Formula I.

Young adult and aged BKW mice are caged in groups of ten in quarters controlled for sound, temperature and

EXAMPLE 19

Intravenous 1-Month Toxicity Study in Rat

5 A. The following describes the procedure for determining the effects of chronic intravenous (i.v.) administration of compounds of Formula I in the rat.

Male and female rats are administered i.v. bolus injections of a compound of Formula I at 0.1, 1.0 and 10.0 mg/kg once daily for 1 month. A separate group of rats are treated similarly with vehicle to serve as experimental controls. .

During the course of treatment body weight, food intake and clinical observations are recorded weekly. Ophthalmologic examinations and urinalysis are conducted during the last week of treatment.

15 After 1 month of treatment all rats are necropsied and clinical chemistry and hematology evaluations of blood samples are performed.

20 B. The procedure described in Part A was carried out for Compound C(HCl) of Example 5A with the following results:

Clinical Observations

25 All rats were clinically normal at all observations.

Mortality

There were no unscheduled deaths during the study.

30 The group average body weights of male rats given 0.1 mg/kg/day of Compound C(HCl) were comparable to vehicle-treated males. Male rats given 1 to 10 mg/kg/day of the compound gained

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5 slightly less weight (5% to 8%) than control males. In contrast, females in all groups treated with Compound C(HCl) gained 17% to 23% more weight than control females. Differences in weight gain of either sex, when present, were not dose dependent.

Food Intake

Food intake was comparable among all groups.

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Ophthalmologic Examinations

No treatment-related ophthalmologic changes were present.

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Clinical Pathology

20 There were no treatment-related differences in hematology or clinical chemistry results in animals given 0.1 or 1 mg/kg/day of Compound C(HCl) or in males given 10 mg/kg/day. Female rats given 10 mg/kg/day had slightly lower erythrocyte counts and hemoglobin and hematocrit measurements than controls. Additionally, females in this group had slightly higher sodium levels than controls. No treatment-related changes in urinalysis data were present.

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Pathology

30 No gross or microscopic pathologic changes of drug-related toxicity were present in male or female rats given 0.1, 1, or 10 mg/kg/day of Compound C(HCl). Liver weights and liver-weight-to-body-weight ratios were higher in females given 10 mg/kg/day than in vehicle-control females.

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C. No undue manifestations of chronic toxicity were observed with other compounds of Formula I.

EXAMPLE 20

ACID ADDITION SALTS

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To a solution of Compound C of Example 5A (about 0.3 kg) in *i*-propanol is added a solution of HCl gas dissolved in *i*-propanol keeping the temperature below 25°C until no more solid precipitates. The solid is isolated and washed with *i*-propanol. The solid is dissolved in *i*-propanol with the aid of deionized water which is subsequently removed by azeotropic distillation. The solution is cooled and aged for at least 2hrs. The product is isolated, washed with *i*-propanol and dried at 50-75°C under reduced pressure. The product may be upgraded by recrystallization from *i*-propanol using deionized water to aid in dissolution. The mother liquor may be reworked by concentration and recrystallization from *i*-propanol with the aid of deionized water for dissolution. The yield of Compound C(HCl) is 60-95%, and the m.p. conforms to that given in Example 5A.

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EXAMPLE 21

PREPARATION OF COMPOUNDS OF FORMULA I WHERE N IS 2,
THE DASHED LINE REPRESENTS A BOND AND R¹ IS A
SUBSTITUENT OTHER THAN HYDROGEN

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A. A solution of 830 mg of (*S*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-2-methoxy-5,6,7,8-tetrahydro-1-naphthalene carboxamide (2.6 mmol) in 75 ml tetrahydrofuran is cooled to -50°C and 6.6 mmol of *n*-butyl lithium in hexane are added. After the addition

is complete the reaction mixture is allowed to warm up to
-20°C for about 30 minutes while a deep red solution is
obtained. The solution is cooled to -40°C and 0.5 ml
dimethyl formamide added in one portion, and then allowed
to warm to room temperature, and quenched with 10%
aqueous hydrochloric acid. The layers are separated and
the aqueous layer made basic with 10N aqueous sodium
hydroxide solution and extracted with ethyl acetate. The
ethyl acetate was dried with brine and anhydrous
magnesium sulfate and evaporated. After flash
chromatography with 5% methanol in dichloromethane and 1%
ammonia 80 mg of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-
9-methoxy-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one
(Compound T) is obtained which is converted to the
hydrochloride salt [Compound T (HCl)] m.p. 270-271°C,
[α]_D²⁵ -21.1° (C 0.27, H₂O): C, 65.74; H, 7.03; N, 7.67.
Found: C 65.48; H, 7.04; N, 7.56] in ethanol hydrochloric
acid/ether.

B. By following the procedure of Part A of this
example with 1.81 grams of the 4-methoxy carboxamide of
Part C of Example 2, 1.6 grams of (S)-2-(1-azabicyclo
[2.2.2]oct-3-yl)-7-methoxy-2,4,5,6-tetrahydro-1H-benz[de]
isoquinolin-1-one are obtained as the hydrochloride salt
[Compound X (HCl)]; m.p. 296/7°C (decomposition)].

C. By following a procedure similar to that of
Part A of this example with 1.02 mmol of (S)-N-(1-
azabicyclo[2.2.2]oct-3-yl)-4-benzyloxy-5,6,7,8-tetrahydro-
1-naphthalene-carboxamide and 2.6 mmol of n-butyl-lithium
and initial cooling to -70°C and cooling to -60°C before
addition of dimethylformamide 110 mg of the 7-benzyloxy
analog are obtained as the hydrochloride salt (Compound S
(HCl)); m.p. 244/5°C.

5 D. A solution of 100 mg (.31 mmol) of Compound X (HCl) of Part B of this example in 5 ml of 48% HBr is heated to 80-90°C for 16 hours and the completion of the reaction monitored with TLC. The reaction mixture is concentrated under reduced pressure, 5 ml dioxan are added and the mixture concentrated again. The residue obtained is dissolved in 3 ml of hot *i*-propanol, the solution is filtered while hot, concentrated to 1.5 ml and stored at room temperature. 40 mg of brown crystals of (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-7-hydroxy-2,4,5,6-tetrahydro-1*H*-benz[de]isoquinolin-1-one hydrochloride are obtained as brown crystals and dried in vacuo (Compound V (HBr) m.p. 319-21°C).

15 E. Using 500 mg of Compound X (HCl) and the procedure of Part D of this example 180 mg of Compound V (HBr) are obtained: $[\alpha]^{25}_D + 41^\circ (c\ 0.02\ H_2O)$

20 F. A mixture of 50 mg of Compound S (HCl) of Part C of this example and 15 mg of 10% Pd on carbon in 7 ml ethanol are stirred under hydrogen for 15 hours at room temperature. The progress of the reaction is monitored by TLC and shows conversion to Compound V which conformed to the compound obtained in Part D of this example. The catalyst is removed by filtration and the filtrate concentrated under reduced pressure. 17.4 mg of 25 Compound V (HCl) are obtained after recrystallization from ethanol.

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EXAMPLE 22

TABLET FORMULATION

5 5% by wt. of Compound C
 69% by wt. of Lactose, spray dried, NF
 25% by wt. of Microcrystalline Cellulose, NF
 1% by wt. of Magnesium Stearate

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Commonwealth of the Bahamas
Registrar General's Department

I certify the foregoing to be a true copy of the
original deposited in this office.

[Signature]
Dep Registrar General
13.5.92